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DIETARY DEFICIENCY AS THE ETIOLOGICAL FACTOR IN PELLAGRA *

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Having expressed the view that pellagra might, like beriberi and scurvy, be caused by a dietary deficiency[1] the writer was invited by the Robert M. Thompson Pellagra Commission to visit them at Spartanburg, S. C., for the purpose of investigating this phase of pellagra. Permission to accept this invitation was granted by the War Department, and the invitation was accordingly accepted. During my short stay at Spartanburg the pellagra commission has put all of their very numerous records and observations at my disposal, has made it possible for me to see a very considerable number of cases of pellagra, and has in every way possible endeavored to facilitate and expedite the investigation. In so far as these observations have any value at all, credit therefor should be awarded to the Robert M. Thompson Pellagra Commission, which has rendered the investigation possible. I also desire to express my indebtedness to several physicians of Spartanburg, but particularly to Dr. O. W. Leonard and Dr. J. H. Allen, who have kindly taken me to see a number of cases of pellagra occurring in their private practice. No one with a proper sense of values can feel that the results of a month's investigation of such a disease as pellagra can be of great importance, but the commission has requested that I present the case for dietary deficiency as I see it.

In the first place it should be stated that I regard the question as to whether pellagra is an infection or a deficiency disease to be entirely open. It does not appear to me that any evidence that can be regarded as proof of either hypothesis has yet been presented. It is rather a question of weighing the evidence and determining toward which

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* From the Army Medical School, Washington, D. C. This paper forms a part of the Third Report of the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

* This report was written in September, 1914.

1. Vedder: Some Further Remarks on Beriberi, Am. Jour. Trop. Dis. and Prev. Med., June, 1914, 1, 826.

hypothesis the bulk of the evidence points. The commission has been inclined to believe rather strongly that it points to the infectious origin of the disease. It seems to me that so far as I have examined it the evidence points at least as strongly toward a dietary deficiency, and it is this side of the case that will be presented here.

In order to understand what we mean by a dietary deficiency in pellagra it will be useful to present as clearly and concisely as possible the conception of deficiency diseases to which recent studies in beriberi and scurvy have led us. Briefly, this conception is that there are certain hitherto unknown chemical substances now called vitamins that are present in small but variable amounts in different foodstuffs, a definite supply of which is absolutely essential to the maintenance of normal metabolism. If a group of people live upon a diet which is deficient in any one of these vitamins, the corresponding deficiency disease is produced in a certain number of these people. Thus, if one hundred soldiers live on an exclusive diet of hard tack and bacon, after a definite depletion period a certain number of these soldiers will develop scurvy, because the scurvy vitamin is either entirely lacking or present in greatly reduced amounts in a diet of hardtack and bacon. If these soldiers are now given either fruits or fresh vegetables which contain this vitamin in relatively considerable amounts, they promptly recover. Equally, men who live on hardtack and bacon, but receive in addition a proper amount of fruit or fresh vegetables, will never develop scurvy.

Passing to beriberi, we find that if a number of people live exclusively on overmilled or white rice, which is deficient in the beriberi preventing vitamins, after a depletion period of about ninety days a certain number of these people develop beriberi. On the other hand, men who receive an undermilled rice which is practically the whole grain, never develop beriberi. It has been found by experimental evidence that the beriberi-preventing vitamins are present in considerable amounts in the external layers of the grain, which are removed in the milling process in the production of ordinary white rice. Furthermore, one of these vitamins has been extracted in crystalline form from the rice polishings removed from the grain, and it has been found that chemically it is probably a pyrimidin base hitherto unknown, but resembling thymin and cytosin in many of its chemical properties.

It should be noted that a deficiency disease is something radically different from malnutrition as the term is generally understood. Thus it is possible that the soldiers living exclusively on hardtack and bacon may have received an adequate amount of proteins, fats, carbohydrates and inorganic salts, furnishing an ample amount of calories, yet they suffered from a disease with a clear-cut clinical picture, namely, scurvy, because of the deficiency of a certain definite chemical sub-

stance which is contained in fruit juices and fresh vegetables. Equally, men living on a daily diet of two pounds of overmilled or white rice, a little meat and cocoanut oil, may receive an adequate amount of proteins, fats, and carbohydrates, according to the acknowledged dietary standards, and yet suffer from a disease with another clear-cut clinical picture, namely, beriberi, because this diet is deficient in certain definite chemical substances, namely, the beriberi preventing vitamins. A deficiency disease is therefore not malnutrition in the ordinary sense, nor is it caused by underfeeding, according to the ordinary standards of physiologists, with regard to a sufficient and properly balanced dietary.

It should also be pointed out that each individual requires a definite quantity of these vitamins. These beriberi-preventing vitamins are present in meat, milk, eggs and similar foods, in relatively small amounts, and in very large amounts in beans, rice polishings, and some other foods. Now, if a number of people live on a rice totally lacking in beriberi vitamins, and in addition consume a definite amount of meat containing beriberi vitamins, which, however, is insufficient in quantity to furnish a sufficient amount of these vitamins, the typical disease will occur in these people, but after a considerably longer incubation period than would have been the case had they lived on rice alone. In order to protect completely from beriberi it is therefore necessary to consume the amount of vitamin essential for that individual's metabolism.

It is further to be noted that because of personal idiosyncrasy the amount of vitamin required is not identical for all individuals. It has been found in feeding experiments on men and animals that of a number of people fed on precisely the same diet, some people develop beriberi much more rapidly than others, while, for some unexplained reason, some individuals never develop it apparently, though these individuals would be exceedingly rare if the beriberi-producing diet were continued for a sufficient length of time.

Now, regarding these statements to be proved facts with respect to beriberi and scurvy, known to be deficiency diseases, we may ask if it is possible to consider pellagra as a deficiency disease? The evidence presented in answer to this query may be considered under the following heads:

1. What analogies exist between pellagra and the two proved deficiency diseases, beriberi and scurvy?

2. Can the evidence pointing toward infection be reasonably explained according to a deficiency hypothesis?

3. Is any deficiency demonstrable in the diets of pellagrins?

4. Can the great increase in pellagra during recent years be explained by the deficiency hypothesis?

ANALOGIES EXISTING BETWEEN PELLAGRA AND BERIBERI OR SCURVY

With regard to the clinical and pathologic phenomena found in these diseases, there are numerous analogies existing between the clinicopathologic picture of pellagra and scurvy, and also between that of pellagra and beriberi, particularly the latter. In pellagra, according to Roberts,[2] "during the outbreak the gums are inflamed, in common with the rest of the oral mucosa. They are tender, often spongy and easy to bleed, as in scurvy; around the lower incisors this condition is most noticeable. During the outbreak stomatitis is present, and reaches its acme at the culmination of the dermatitis and glossitis. The inner borders of the lips and cheeks are red, tender, raw and swollen, and this inflammation extends over the buccal mucosa to such an extent that eating and swallowing are difficult."

With regard to scurvy, Osler[3] says: "Very soon the gums are noticed to be swollen and spongy, to bleed easily, and in extreme cases to present a fungous appearance. These changes, regarded as characteristic, are sometimes absent. The tongue is swollen, but may be red and not much furred." The mouth condition, therefore, while not at all identical in the two diseases, at least presents a certain similarity.

The gastro-intestinal lesions in pellagra and scurvy are analogous. In pellagra we have diarrhea, enteritis, colitis and proctitis. "As the disease advances, the entire alimentary tract becomes inflamed; gastritis, enteritis, colitis and proctitis are the foundations for gastric and intestinal ulceration, with blood, mucus, pus and increased putrefaction and fermentation."[2] "With acute cases and enteritis, ulceration may occur at any part of the large or small gut."[2]

In scurvy, "Ulcers are occasionally met with in the ileum and colon. Hemorrhages, into the mucous membranes are extremely common."[3]

There are similar nervous symptoms in pellagra and scurvy. In pellagra the mental symptoms are so pronounced and well understood that it is unnecessary to quote authorities. In general, they consist of retardation of the mental processes and a general feeling of depression that may shade into melancholia or other psychoses. In scurvy, "there are mental depression, indifference, in some cases headache, and in the later stages, delirium."[3] Osler mentions scurvy as one of the diseases from which pellagra must be differentiated. No attempt is being made here to show that the two diseases are at all identical, but

2. Roberts: Pellagra, C. V. Mosby Co., St. Louis, 1912, pp. 30, 109, 117, 119.

3. Osler: The Principles and Practice of Medicine, Ed. 8, D. Appleton & Co., New York, 1912, p. 447.

to point out that there are certain resemblances in their symptomatology and pathology.

Suggestive similarities also exist between pellagra and beriberi. Thus we find that in beriberi the mucous membrane of the stomach and duodenum is frequently swollen and inflamed, with a high degree of hyperemia and numerous ecchymoses and erosions. It may be remembered that Hamilton Wright thought that the cause of beriberi was a primary duodenitis caused by an invading bacillus. The pathologic process found in the duodenum in beriberi is often, therefore, somewhat similar to the condition of the intestine in pellagra, though the lesion never appears to progress so far or to be so extensive in beriberi as in pellagra.

Similarities in the lesions in the nervous system and in the symptomatology referable to the nervous system in pellagra and beriberi can be distinguished. The pathologic alterations that occur in the cord in pellagra are profound and striking. Extensive degenerations have been described in certain cases in the posterior column and in the pyramidal tract, as well as more or less diffuse degenerations. It is of course possible that certain of these cases of pellagra may have suffered at the same time with well-known nervous diseases, such as tabes dorsalis or multiple sclerosis. It seems clear that a definite sclerosis cannot occur in pellagra, since the majority of pellagra cases recover, and this would be an impossibility if an actual sclerosis of the cord were present. But it seems certain that a majority of the cases of pellagra suffer from a certain degree of degeneration of both the cells and the fibers of the cord, because of the great constancy with which these lesions are found in cases at necropsy, and because almost all cases of pellagra show symptoms that are referable to changes in the cord. A few quotations will serve to illustrate this point. The following is from Roberts:

> 1. Tracts: The tracts of Goll and Burdach show degeneration and a profuse proliferation. These tracts are pale compared with the rest of the cord. Occasionally degenerate roots entering in lumbar region can be traced up into the dorsal region. There may be degeneration of the posterior roots and an increase in the connective tissue around these roots, with occasional thickening of the arteries. The degenerate areas in stained preparations show like small spots of ink spattered all over the posterior column.
>
> 2. Direct pyramidal tract: There is more or less degeneration and scattered areas from which the nerve fibers have disappeared. Occasionally swollen axis cylinders are found (Spiller).
>
> 3. Gray matter: There is pigmentation of the cells of the anterior and posterior horns. The reticulum of many of the cells is clearly evident, and the fibrils appear contracted and the cell smaller. The cells of the posterior horns appear degenerated from the cervical region downward, and especially are the cells in Clarke's column affected. Spiller found cells in the anterior horns in the lumbar region degenerate, the cell body swollen, the nucleus displaced to the periphery, dendrites gone and intense chromatolysis, etc.

The following quotation is from a necropsy on a patient dying of pellagra, from the report of the pellagra commission of the state of Illinois, 1911, page 29:

> Nerve cells: Sections were examined from various regions of the cortex and also from different levels in the cord and medulla. Stained with methylene blue and cresyl violet, marked chromatolytic changes of an axonal type were found in the large pyramidal cells of the rolandic region, but especially of the Betz cells. Of these latter, practically all show extreme changes. The cells are swollen and stain faintly, the nucleus is displaced and the nucleolus often stains poorly. The Nissl granules have largely disappeared, small collections of them remaining at the base of the larger processes along the edges of the cell, and often collected as a small mass around the nucleus. . . . In the spinal cord similar changes are found in some anterior horn cells at all levels examined, but the great majority of these cells appeared healthy. The most marked changes were found in the cells of Clarke's column, where the majority of them were undergoing chromatolysis and pigmentary degeneration. Chromatolytic changes were also found in the cells of the posterior root ganglia. . . . Marchi method: In the spinal cord there are a few degenerated fibers scattered diffusely through the white matter. Degenerated fibers are also present in both anterior and posterior spinal roots.

Now, if we compare this picture with the changes found in the cord in beriberi, we find that beriberi is characterized by the same scattered degeneration of fibers in the cord and similar changes in the cells of the cord.[4] The anatomical changes found in the brain in pellagra have not been demonstrated in beriberi, but Funk[5] has shown that chemical changes occur in the brain of fowls that have developed polyneuritis as the result of rice feeding.

Beriberi has for years been regarded as essentially a disease of the nervous system. This conception of beriberi is hardly correct, since it is essentially a deficiency disease, resulting in numerous bodily changes. But it appears that pellagra is quite as much essentially a disease of the nervous system as is beriberi. The following quotations illustrate this point:

> There is a general conviction that pellagra is especially a disease of the nervous system. Wood[6] says: "It is daily a problem with me and my colleagues to differentiate between myelitis of specific origin and similar pathologic conditions produced by pellagra."
>
> Pollock and Singer[7] show that many of the severe and fatal cases present the syndrome of central neuritis, which is a reaction of the central nervous system to severe intoxication.
>
> Dr. E. B. Saunders very kindly furnished me with information as to the mode of death among pellagrins in the Columbia State Hospital. According to her

4. Vedder: Beriberi, Wm. Wood & Co., New York, 1913, pp. 37, 39, 42, and Plate V.

5. Funk: The Effect of a Diet of Polished Rice on the Nitrogen and Phosphorus of the Brain, Jour. Physiol., 1912, xliv, 50.

6. Wood, E. J.: Treatise on Pellagra, D. Appleton & Co., New York, 1912, p. 228.

7. Pollock and Singer: The Histopathology of the Nervous System in Pellagra, THE ARCHIVES INT. MED., June, 1913, xi, 565.

observations in a series of eighty-eight fatal cases, sixty-four, or 74.7 per cent., died with central neuritic symptoms; nineteen, or 21.6 per cent., with appearances of simple exhaustion, and five, or 5.6 per cent., terminated suddenly from some unknown cause. In all severe cases there are evidences of irritable weakness in the nervous system, such as tremors, exaggeration of tendon jerks, increased myotatic irritability, etc., entirely comparable to those met with in other severe intoxicative conditions, such as tuberculosis.[8]

It was exactly such changes in the nervous system that caused beriberi to be considered for many years as an intoxication. Now that we know that beriberi is a deficiency disease, it is apparent that these changes in pellagra are quite as likely to be due to deficiency as to intoxication or infection. The fact that the spinal fluid in pellagra is normal, points toward deficiency, since it seems improbable that such extensive changes in the cord could occur as the result of an infection without producing the corresponding changes in the spinal fluid. Even the skin lesions which are so characteristic of pellagra may be referable to changes in the cord. Otherwise, how can we explain the marvelous symmetry that is practically the constant characteristic of this symptom?

But without attempting to strain the analogy, enough has been said to show that pellagra shows marked similarities in both pathology and symptomatology to beriberi and scurvy, two deficiency diseases. While it would be foolish to assume that therefore pellagra must also be a deficiency disease, this possibility is at least suggested, while on the other hand it may be stated that there is nothing in the pathology or symptomatology of pellagra of such a nature as to render it impossible to conceive of their production as a result of a dietary deficiency. Similar and equally marked changes are produced as the result of two known deficiency diseases.

Analogies exist between the epidemiologic data in pellagra and beriberi. Pellagra, like beriberi, is a disease intimately associated with poverty and poor diet. The present commission has classified 277 cases of pellagra according to economic conditions as follows:

Squalor	2
Poverty	28
Necessities	200
Comfort	41
Affluence	6
Total	277

This is sufficient to show that among the people at large its distribution is chiefly among the poorer classes. It is admitted by the commission that the diet of these poorer people is far from satisfactory,

8. Singer: Mental and Nervous Disorders Associated with Pellagra: Second Progress Reports, Thompson-McFadden Pellagra Commission; The Archives Int. Med., 1915, xv, 121.

and the commission is inclined to lay a great deal of stress on the importance of diet as a contributory factor in the production of pellagra.

Like beriberi, pellagra shows an extraordinary frequency in hospitals for the insane and in similar institutions where a large number of people live under comparatively good sanitary conditions, but where the diet is by no means above reproach. At the same time, like beriberi, it is exceedingly rare for doctors, nurses or attendants, living in close personal contact with these cases, but on a different dietary, to acquire pellagra. Thus Singer[8] says.

> Pellagra shows an extraordinary frequency in hospitals for insane. This fact of almost universal experience is well illustrated by the situation at Milledgeville, Ga. If we accept the proportion of certifiable insanity for Spartanburg County as approximately correct for the state of Georgia, this would mean that in 1910 there were approximately 900 pellagrins (this figure is probably far too small), or 3.4 per 10,000 of the population. On the other hand, the average daily population of the hospital was 3,276, with 114 cases of pellagra, or 348 per 10,000, practically 100 times as many as in the population outside. Experience in Illinois would tend to bear this out. There are several possibilities:
>
> 1. If infectious, these hospitals are endemic foci with favorable opportunities for transmission.
>
> 2. Deficient dietary or food intoxication may exist.
>
> 3. Conditions of life-or constitution of persons confined in such a hospital may be such as to especially favor the onset of pellagra, whether the cause be a living virus, deficiency or intoxication.
>
> In discussing these possibilities, it must be conceded that the only explanation for a special focus of infection in such a hospital would be the collection together of a large number of infected individuals sent to the hospital because of the occurrence of "insanity." This would not explain the sequence of events at the Peoria State Hospital and other institutions of like character in Illinois where the outbreaks appeared to start in these widely separated localities while the number of cases in the state generally was certainly small.
>
> Some explanation is also needed for the rarity with which doctors or attendants in these institutions become affected. I know of no instance in Illinois. In Georgia but one was reported (J. E. H., white male attendant, on June 19, 1913) in the years from 1910 to July, 1913.

It appears, therefore, that it is extremely difficult to account for the peculiar distribution of pellagra in these institutions on the basis of an infection, while it is rather easy on the hypothesis of a dietary deficiency. As a matter of fact the dietary at Peoria was admitted to be poor, and soon after it was radically improved pellagra disappeared.

Still further, as Singer says:

> It is quite within the bounds of possibility that the actual relation between the functional psychoses (including dementia praecox) and pellagra is somewhat the reverse of that more usually accepted. That the defective construction, whatever it be, which is responsible for the poor adaptability and peculiarity of make up, indicated by the particular stamp of these disorders, predisposes to the development of pellagra. It is certainly a fact that the disease is extremely frequent among the chronic insane, most of whom represent late stages of the dementia praecox personality.

This is exactly what Bondurant[9] found to be the case with regard to the distribution of beriberi at the Alabama Bryce Insane Hospital. Every one of the seventy-one patients attacked was the subject of some psychic degenerative form of mental disorder. It is apparent, therefore, that there is some close relation between such psychic states and a tendency to acquire a deficiency disease. A possible explanation of this fact is the well-known indisposition of many such patients to eat a correct or sufficient diet. This hypothesis would explain Singer's observation of the tendency of this class of persons to develop pellagra.

In Italy at least, pellagra appears to bear somewhat the same relation to the consumption of corn that beriberi bears to the consumption of rice. The striking analogy, which every one admits, and which has led the Italian investigators for many years to believe that pellagra is caused in some way as the result of a corn diet, needs no further discussion.

The theories promulgated as to the cause of pellagra bear a striking resemblance to the history of the investigations into the cause of beriberi. Like beriberi, when first discovered many attributed it to an improper diet. After finding apparent inconsistencies in this explanation, in each disease the pendulum has swung to intoxication, infection, and finally back to deficiency again. Pellagra, like beriberi, has been investigated carefully for a number of years in the endeavor to discover some micro-organism or toxin responsible for this condition. All such efforts have been futile. This, of course, like other analogies, proves nothing, but it is at least suggestive. Such analogies might be multiplied and carried farther, but no good purpose would be served by doing so, since no definite evidence is to be obtained in this way.

CAN THE EVIDENCE POINTING TOWARD INFECTION BE EXPLAINED ON THE DEFICIENCY HYPOTHESIS?

Let us look into the character of the disease. The peculiar pathology and symptomatology of pellagra has undoubtedly caused some observers to come to the conclusion that pellagra is a toxemia or is infectious. At first glance it does seem difficult to believe that such pronounced lesions can be caused by a mere dietary deficiency. But we have already discussed the resemblances in the pathology and symptomatology of pellagra as compared with beriberi and scurvy and have come to the conclusion that if dietary deficiency can produce the pathologic condition observed in beriberi and scurvy, it is quite possible that a different deficiency could produce the changes observed in pellagra.

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9. Bondurant: Report of Thirteen Cases of Multiple Neuritis Occurring Among Insane Patients, Med. News, London, 1896, lxix, 365; Endemic Multiple Neuritis (Beriberi), New York Med. Jour., 1897, lxix, 685, 728.

But beyond this, the definite tendency seen in pellagra to self-limitation of the attacks in the absence of specific therapy, and during the continuance of presumably the same defective diet that produced the disease, appears to some to bear a very suggestive resemblance to the course of an infectious disease. Most decidedly an opinion exists that if the disease were due to a deficiency, it could not be self-limited while the deficiency exists. But is pellagra really self-limiting while the deficiency exists? Granting for the sake of argument that pellagra is a deficiency disease, we have been in total ignorance as to which foods contain the necessary vitamins and which foods are totally deficient. How then is it possible to say that the patient has not received some nourishment which has supplied the deficiency and that the improvement is not in reality due to this fact? It would not be possible to make such a statement except in the case of a patient fed on water alone, and such cases must be exceedingly rare. If the patient is in such condition as to make it possible to take only liquid nourishment, he still can and probably does receive soups, milk, albumin water and similar diets, any one of which may, so far as we know, be responsible for the change for the better.

The converse of this proposition has also been stated, namely, that patients with pellagra sometimes become worse and often die in spite of the fact that they are receiving a most excellent diet. But while it may have been an excellent diet generally speaking, it may not have been particularly rich in the necessary vitamins, or the patient may have been unable to assimilate them. Further, we know that patients with dry beriberi often become worse and die, even though they be fed on beans, rice polish and other substances that we now know will prevent the development of beriberi. This is a well authenticated fact, and the probable explanation is that the lesions in the cord and nervous system generally have proceeded to such a point that death is imminent and may occur at any time. In this form of beriberi the road to recovery is long and up hill, and on any diet only occurs after several months. It is clear, therefore, that the patient may die before the slow process of recovery has succeeded in patching up his serious lesions. Is not the same thing conceivable and even probable in pellagra, granting that it is a deficiency disease? Aside from theoretical reasoning, it is an observed fact that beriberi patients have their ups and downs either in their natural surroundings or in a hospital. In some the disease appears to be quite as naturally self-limited as is the case in pellagra. Manson describes this in his most graphic and charming style as follows.

As the visitor watches the progress of the cases he will be astonished that those which he thought examples of locomotor ataxia, or of progressive muscular atrophy, or of ascending spinal paralysis, gradually improve, begin to walk about,

and finally quit the hospital quite well. He will be astonished to see, after perhaps a profuse diuresis, the bloated carcass that could hardly turn itself in bed rapidly shrivel to little more than skin and bone, and assume all the appearances of the atrophic cases; and later, perhaps after many months, become rehabilitated, and, in due course, walk out of the hospital quite well. He will notice that the cardiac bruits come and go; that the degree of dilatation of the heart is subject to fluctuations; that what seemed organic disease completely disappears. But he will also be astonished, as he goes his rounds, to see so often empty beds where the day before lay men whom he considered by no means seriously ill, certainly not dying. Some day he will come on a patient whom the previous day he thought to be by no means seriously ill, actually in extremis. The poor fellow is propped up in bed, is struggling for breath, his face is purple, his eyes are starting out of his head, his whole attitude is expressive of the utmost distress—in a short time the patient is dead.

This account was written prior to the days when the relation of diet to beriberi was known. I have no doubt that Manson would have thought that all of his patients were receiving an excellent diet, yet some of them recovered, and some died in a most unaccountable manner. It is probable that at this day we cannot explain all of these peculiarities by demonstrated changes in the patient's diet. Some must be ascribed to the personal peculiarities of the patient and to the particular pathologic changes that have occurred in that patient. In view of the fact that beriberi has acted in this peculiar way, shall we say when we observe the same kind of peculiar and unexplainable occurrences in pellagra that this points toward infection? By no means. It points equally or more toward a deficiency disease that acts just as beriberi acts.

But again, it is objected that pellagra appears in the spring and improves during the summer and fall, only to recur again next spring. This fact appears to point distinctly toward the dietary hypothesis. The peculiar tendency to recurrence during the late spring, May or June, if explained according to the infection theory, presupposes an infection that acts differently from any known infection; one that is dormant during the winter months only to break out with fresh fury in the next spring, and not only once, but again and again. It is safe to say that we know of no infection at present that acts in this way; but beriberi acts in precisely this fashion. It not only appears more commonly during certain well-known seasons of the year, but individual patients are subject to frequent recurrences during these seasons. The dietary habits of the people undergo considerable change with the seasons. For instance, in the general population more meat is eaten in the winter than in the summer. But is it not quite possible that during the winter the poor, who suffer chiefly from pellagra, live mainly on flour, cornmeal, canned beans, salt pork, etc.; that they are thus subject to a deficiency, which, after a depletion period of several months, produces lesions in the spring; and that when fresh vegetables and fruits appear in the market in the spring and summer the con-

sumption of such food supplies the deficiency, and the disease improves, only to recur in the following spring after the patient has once again been subject to the same deficiency? This conception is at least as plausible as the conception of an infection that can produce such peculiar seasonal recurrences with intervals of apparently perfect health.

Is contact or personal association with cases of pellagra an etiological factor? In about 90 per cent. of the cases of pellagra studied, this commission has established the fact that some degree of personal contact or association with a previous case of pellagra can be traced. This fact, which at first glance appears to argue strongly in favor of the infectious nature of the disease, is in reality of little significance. For in the first place a large number of these contacts, 43.5 per cent., have occurred among members of the same family, who have presumably lived upon the same diet, and if the cause of pellagra were a dietary deficiency it would be expected that several cases would frequently develop in one family. With regard to the remainder of these cases, 46.5 per cent., in which contact with an antecedent case outside the family has been demonstrated, it must be pointed out that pellagra has become so common in many parts of the South that practically every one has come into some contact or association with a case of pellagra. Pellagrins ride in the street cars, they peddle vegetables and fruits, they frequent moving pictures and other public gatherings and come in contact with normal individuals in all the numerous ways possible in our society. The fact that a very large part of the population has in these ways been in contact with cases of pellagra without developing the disease necessarily detracts from the importance of contact as an etiologic factor. Further, in institutions those persons in closest contact with pellagrins, namely the doctors, nurses and attendants, seldom acquire the disease.

Is the tendency of pellagra to vary with the density of population an indication of infection? The commission says:[10] "The conception that pellagra is an infectious disease in some way transmissible from person to person seems to us to be strongly supported by many of the field observations. The higher incidence of pellagra in the more populous districts and the indications of its occurrence in definite foci are in accord with this idea." They find that the cotton mill village population gives a rate of prevalence of 184 per 10,000 against 19 per 10,000 for the remainder of the county and against 16 per 10,000 for the rural sections alone. It is only fair to add that on page 26 the commission says: "Further evidence that density of population alone is not accountable for the greater prevalence of the disease in mill villages is found in Spartanburg City itself. There the mill villages,

10. First Progress Report, Thompson-McFadden Pellagra Commission, p. 11.

which are continuous with and an integral part of the city, present a rate of 142 per 10,000, whereas the remainder of the city population, living under approximately the same condition of congestion, gives only 29 per 10,000. Furthermore, the non-mill-village population within the city, with a density which is certainly over 3,000 per square mile, shows almost exactly the same prevalence of pellagra per 10,000, as does the strictly rural population of the surrounding township, with only 90 inhabitants per square mile." This seems to me to definitely dispose of the idea that density of population alone bears any relation to the spread of pellagra. It should furthermore be noted that many authorities claim that pellagra is distinctly a rural disease and stops abruptly when it reaches cities.[2] It may be mentioned in passing that the higher incidence of pellagra in the mill villages would be readily explainable according to the deficiency hypothesis by assuming that the mill village population was a rather homogeneous group of the community, and as a group, is poorer economically and lives on a poorer class of food. As a matter of fact, this assumption is correct. The occurrence of the disease in definite foci does not therefore afford any proof that density of population alone influences the incidence of pellagra.

Is proximity of domicile a factor in the occurrence of pellagra? The most important evidence collected by the commission pointing toward the infectious origin of pellagra is its study of the domicile of cases. The commission shows that of 819 nonpellagrin individuals who lived in the house where pellagra existed at the time, fifty-four, or 6.59 per cent., acquired pellagra, while in the 3,201 nonpellagrin individuals who lived next door to a house in which pellagra existed, fifty-five, or 1.72 per cent., developed pellagra; of the 3,105 persons who lived in houses farther away than next door to a pellagrin, sixteen, or 0.52 per cent., contracted the disease. The new cases of the disease developed almost exclusively in small foci within which one or more cases of the disease already existed.

Can this incidence of cases be explained if the disease is not infectious, but caused by dietary deficiency? In the first place it will be at once seen that zone 1, in which 6.59 per cent. of the exposed individuals acquired pellagra, consists of those people living in the same house with a pellagrin. If the disease were of dietary origin, the majority of the inhabitants of this house, presumably living on approximately the same diet, would all be exposed to the same deficiency, and a high proportion of additional cases would develop. The considerable number of cases occurring in the first zone can therefore be explained quite as easily in accordance with the dietary as by the infection hypothesis. But with this zone eliminated, the domiciliary argument has lost much of its force, since only two zones are left and the inci-

dence of pellagra in the second zone was only slightly more than three times as frequent as the third zone. A possible explanation for the higher incidence of cases in the second zone may be as follows: Pellagra is much commoner among the poor than among the well-to-do. Now in all of these villages there is probably a natural tendency for the well-to-do to live in certain parts of the village, and for the poorer workers to live in certain localities and streets. This is a human tendency which may be less marked in mill villages than it is among the population of a city, but still it exists. The reason for this segregation of the poor lies in various economic factors, such as possibly the cheaper rent in one section of the town, and also in the tendency for like to seek like. Well-to-do people naturally select a house next to well-to-do neighbors, rather than next to a poverty-stricken neighbor. This is a human tendency that is just as definite as the tendency for water to seek its level. There is, further, in most of these towns a considerable proportion of floating population. These people do not reside permanently at any one mill, but move from mill to mill as they become discontented. A very considerable proportion of the wages of these transients is consumed in their frequent moves, they are generally a less efficient type of worker and receive on this account smaller wages, and they are, as a general rule, distinctly lower in the economic scale than the permanent residents. In many of the villages a certain street or locality is set apart for new comers, and they are only permitted to move to a better part of the town after they have "made good." Now if this tendency of the poor to become segregated be granted, and if pellagra is due to a dietary deficiency, it follows that it will occur most often in the streets or localities more frequented by the poorer workers, and less frequently among those streets and localities inhabited by the well-to-do. And if such a grouping of the population and of the disease occurs, the second zone, namely, the houses contiguous to a case of pellagra, would naturally show a higher incidence of the disease than the houses at a greater distance. The zone distribution of cases of pellagra in such villages cannot afford any conclusive evidence that the disease is an infection, while it is possible of explanation on the other hypothesis.

Moreover, it appears to me that to accept this zone distribution of cases as pointing to an infectious agent as the cause of pellagra involves us in an inconsistency. We must necessarily assume that the infectious agent is conveyed in some manner from house to house, and also, from the frequency with which contiguous houses are attacked that it is susceptible of being distributed with a considerable degree of certainty. In other words, we must assume that the organism causing the disease must be very highly infectious if it is capable of making it dangerous to live next door to a case of pellagra. Yet

in institutions pellagra in a doctor, nurse or attendant is so rare as to be a curiosity. We have then an infection so powerful that it often spreads from house to house, and yet which is powerless to attack attendants performing the most intimate of personal services. Such a peculiar incidence is conceivable in a disease carried by an insect, if the hospital attendants were protected from that insect. But as the method of transmission is unknown, measures to prevent insect transmission could not have been intelligently adopted in these institutions, many of which are infested with bedbugs, lice, biting flies and mosquitoes.

Is there a tendency of pellagra to occur in that part of a community having a primitive system of disposal of excreta and to be absent in the portion having a proper sewer system? The commission has shown that pellagra in Spartanburg is much commoner in those sections of the city having privies than in those sections of the city having a sewer system. The sewer system runs throughout the business sections and better residence districts, while the poorer residence districts, including the several foci of mill workers, are supplied with unscreened privies. Since, in general, it is the poor people who have the privies, it is apparent that poverty and a poorer dietary cannot be excluded as the possible factor producing the disease. The commission points to the epidemic of pellagra occurring in Peoria as an instance of the occurrence of the disease in a well sewered institution, but thinks that the disease in this case may have been spread by contact. While freely granting this, we must see that the occurrence of such an extensive epidemic of pellagra in a well-sewered institution must necessarily detract from the importance of the sewer system alone as a factor in reducing the prevalence of pellagra in the sections of Spartanburg it supplies. It should further be remembered that as pellagra in the Peoria institution disappeared after a radical change for the better had been made in the dietary, together with the enforcement of segregation of pellagrins, the disappearance of the disease can not logically be attributed to the latter factor alone. I realize that this brief discussion of one or two isolated instances can not do justice to the large number of observations accumulated by the commission on this point, but I think that the commission does not believe that they have any direct proof that pellagra has disappeared as the result of improved methods of conservancy alone.

The commission has been inclined to believe that the disease is not of dietary origin because their investigations have failed to implicate any special food as the causative factor.[11] Thus, in the case of beriberi,

11. Siler, Garrison and MacNeal: A Statistical Study of the Relation of Pellagra to Use of Certain Foods and to Location of Domicile in Six Selected Industrial Communities, THE ARCHIVES INT. MED., 1914, xiv, 293.

in those countries where the disease is endemic, it is very closely associated with the consumption of overmilled rice. No such striking parallel has been brought out by the observations of the commission in this country. Corn, of course, has been implicated in other countries, particularly in Italy, but the commission has shown that in this country the incidence of pellagra is relatively higher among those using cornmeal rarely or never. Thus, of those using cornmeal daily, 3.13 per cent. were pellagrins; of those using it habitually, 4.3 per cent. were pellagrins; and of those using it rarely or never 6.02 per cent. were pellagrins. Obviously, they think that corn as a causative factor must be dismissed from further consideration. Similarly, they find that of eighty-nine persons using canned foods daily, none were pellagrins; while of those using these foods habitually, 3.25 per cent. were pellagrins; and of those using them rarely or never, 4.12 per cent. were pellagrins.

Again, if the disease were a deficiency disease, fresh meat, milk and eggs might be supposed to supply this deficiency. They found, however, that of the eighty-two persons in families using fresh meat daily, four, or 4.88 per cent., were pellagrins; of the 2,591 individuals in families using this food habitually, 3.74 per cent. were pellagrins; and of the 263 persons never using fresh meat, only four, or 1.52 per cent., were pellagrins. Similar figures were obtained with regard to the use of eggs. The commission is therefore inclined to believe that the disease is not caused by a dietary deficiency.

It appears to me that this evidence is not at all conclusive for the following reasons: 1. It does not consider in sufficient detail the quantities of the various foods used. In an investigation of this kind it is important to know the relative quantities of the different foodstuffs used. It has been found in the course of experimental work on beriberi that if fowls are fed exclusively on overmilled rice, they develop polyneuritis after about thirty days. Now if in addition to polished or overmilled rice these fowls are fed 10 gm. of meat daily, it was found that these fowls developed polyneuritis with just as much certainty, but only after a longer depletion period, about fifty days. In other words, the meat contained a certain amount of protective vitamins. If consumed in sufficient quantity, it would have protected the fowls completely against the disease. But 10 gm. was a quantity insufficient to afford this complete protection. The fowls still suffered from the same deficiency, though not to so pronounced a degree, and the clinical manifestations of the disease therefore appeared after a longer depletion period. Experience has shown that a similar relationship exists with regard to the quantities of foods consumed and beriberi in man.

If pellagra is a deficiency disease, a similar relation undoubtedly exists between the occurrence of the disease and the quantities of certain foodstuffs consumed. Thus, let us suppose that the disease is caused by a deficiency occurring in wheat flour and that the chemical substance or vitamin deficient in wheat flour is present in a certain small amount in eggs. It follows that if a man ate a pound of bread and an egg daily he might still suffer from the deficiency because one egg would contain an insufficient amount of vitamins to make up for the deficiency in the flour. On the other hand, if the man ate a pound of bread and four eggs daily, he might be completely protected.

Now in their dietary study the commission has classified the users of various foodstuffs into those eating them daily, or habitually, and those eating them rarely, or never. This, however, is by no means the same as an exact quantitative determination of the amounts of food used. The man referred to above could have honestly stated that he ate eggs daily, and this may have happened in a considerable number of instances, which might explain why pellagra was found to be frequent among those who used eggs daily. The Filipino who develops beriberi does not live on rice alone. He also eats a small quantity of fish. Many of them eat two pounds of rice daily, and at each of the three meals will also eat a fish the size of a small herring. This man eats fish daily, yet he develops beriberi. Are we therefore to conclude that because he eats fish daily and develops beriberi that fish can be of no importance in preventing beriberi? It is impossible to draw conclusions as to the relative value of different foodstuffs in preventing a given disease except from a quantitative study, and such quantities are not supplied by a statement that the food under consideration is eaten daily or habitually; in fact such observations may be exceedingly misleading.

2. In the commission's study of the diet a very large number of individuals have been consulted with regard to their use of certain foods. When these statistics have been compiled, each foodstuff has been considered singly, that is, the influence of corn meal or of eggs, etc., with regard to pellagra has been considered separately. But in order to determine if the diet consumed by a given individual is deficient, the total diet must be considered, or otherwise an erroneous conclusion may be deduced. For instance, we may find that five individuals consume corn meal daily and none of them suffer from pellagra, while five other individuals never consume cornmeal and all five have pellagra. Shall we assume that cornmeal is of no importance in relation to pellagra? This would be erroneous, because the five individuals eating cornmeal daily may also eat a large number of other foods which supply the deficiency, while those who never eat cornmeal and develop pellagra may be living too exclusively on some other food,

such as wheat flour, which is also deficient in proper vitamins. Evidently, therefore, in any community such as this, where a considerable number of different foodstuffs are consumed by the population, an idea as to the existence of a deficiency can be obtained only by considering the total diets of individuals suffering with pellagra as compared with total diets of the healthy part of the population, and not by the consideration of single items of the dietary.

3. The commission has not discussed sufficiently the possibility that wheat flour is the foodstuff that is mainly responsible for the deficiency. They say: "Wheat flour was used daily by every family in the population studied. No distinction between pellagrins and nonpellagrins could be ascertained in respect to this dietary element." It appears to me, as will be seen farther along, that wheat flour is certainly an excessively large component in the diets of the pellagrins studied, as compared with the relative amounts of other foods used. Flour has long been known to be deficient in the scurvy vitamins. It has been shown by Little[12] that white wheat flour is deficient in the beriberi-preventing vitamins. Is it not also possible that if pellagra is a deficiency disease it is also deficient in the pellagra vitamins?

None of the evidence discussed here is of such a nature as to enable us to say that pellagra is not infectious or is a deficiency disease. But it does seem to me as if the commission is inclined to dismiss the dietary deficiency hypothesis from further consideration a little too hastily.

IS THERE DEFICIENCY IN THE DIET OF PELLAGRINS

With these conditions in mind, the investigation was focused in an attempt to determine whether any deficiency could be demonstrated in the diets of pellagrins. For this purpose a number of pellagrins were visited and inquiries made as to their diet, and particularly with regard to their diet during the winter preceding the first attack of the disease. The information so obtained may be summarized as follows:

The diet of pellagrous mill workers and other relatively poor individuals was investigated as follows:

Case 1.—Miss T., mill operative: Breakfast: Hot biscuit, butter and molasses; rice occasionally; canned salmon frequently; eggs a couple of times a week; coffee; glass of milk at times.

Dinner: Meat, usually bacon boiled with vegetables; had fresh beef once or twice a week, fried and usually overcooked; chicken or rabbit about once a month; had vegetables, such as Irish potatoes, sweet potatoes; in winter used canned vegetables, but in summer had string beans, corn, peas, onions, etc.; cornbread made of shipped meal.

12. Little: Beriberi Caused by Fine White Flour, Jour. Am. Med. Assn., 1912, lviii, 2029.

Supper: Cornbread and buttermilk; drank about a quart of milk daily (her estimate); ate a good deal of candy and always had plenty of fresh fruit. This family (father and mother and seven children from 20 years of age to 13 months) purchased each month: 100 pounds wheat flour, 2 bushels corn meal, 1 bushel Irish potatoes, hominy and rice as desired from time to time, and no account kept.

Case 2.—Mr. T., father of Miss T.: Will not eat fresh beef, but otherwise eats the same diet as given above.

Case 3.—Mrs. H., housewife in mill village: Breakfast: Biscuits or bread; salmon twice a week, other mornings bacon; coffee; eggs rarely.

Dinner: Tomato soup; salt pork boiled with vegetables, usually cabbage, sometimes string beans; Irish potatoes; fresh meat only on rare occasions in the winter, never in summer; biscuit or corn bread.

Supper: Bread with milk when they can get milk; bread is the main part of supper with anything left over from dinner; occasionally something canned. There are nine in the family, with seven children from 14 years to 4 months, and they purchase every month: 100 pounds flour, 1 bushel corn meal, 1 peck Irish potatoes.

Cases 4 and 5.—Bertha, aged 9, and Bessie, aged 6, children of mill operative. Breakfast: Bread, butter and molasses; canned salmon occasionally; eggs once every two weeks or a month; coffee.

Dinner: During winter have a little steak or fresh pork occasionally, otherwise no meat; dinner consists chiefly of Irish potatoes with boiled vegetables, usually cabbage; cornbread or biscuits; a glass of milk.

Supper: Cornbread and one glass of milk with everything left from dinner; fruit in summer, but none in winter. For the seven in the family, five children from 16 to 4 years of age, they purchase each month: 75 pounds flour, 2 bushels cornmeal, 3 pecks of potatoes.

Case 6.—Mrs. B., housewife of mill operative: Breakfast: Biscuit, butter, jelly and syrup; coffee, bacon and eggs every week or two.

Dinner: Chicken three or four times during winter, otherwise no meat except salt pork; potatoes, cabbage or beans, tomatoes once in a while; cornbread.

Supper: Cornbread and what is left from dinner. For the eight members of the family, six children from 18 to 4 years, they purchase each month: 50 pounds flour, 1 bushel cornmeal, 2 pecks of potatoes.

Mrs. B. came from a farm on January 29 and developed pellagra about June. When she lived on the farm her diet was as follows:

Breakfast: Biscuits, butter; one or two eggs once or twice a week; chicken every week or two; fresh pork occasionally at hog killing.

Dinner: Had more vegetables than above, and one glass of buttermilk every day; had more fruit than now.

Supper: Same as above, except that she always had plenty of milk. She says she lived better on the farm.

Case 7.—Mrs. B., wife of mill operative: Breakfast: Rice, oatmeal occasionally, hominy frequently, bread, butter and jelly; coffee; eggs several days a week; in winter fresh meat once a week.

Dinner: Irish potatoes, bacon and vegetables, beans, peas or turnip greens; bread and butter.

Supper: Irish potatoes, cornbread sometimes, otherwise wheat bread, butter, and anything left from dinner; drinks no milk; has a chicken occasionally, but not often.

Case 8.—Mrs. D., wife of mill operative: Breakfast: Hominy or oatmeal; ham or bacon; eats an egg perhaps two mornings a week; bread, butter and postum. Says chief part of her breakfast is always bread and butter.

Dinner: Irish potatoes; in winter has beans; says she does not care for meat and practically never eats it; bread and butter and usually pie or cake; main part of dinner is the beans and potatoes.

Supper: Same as dinner; drinks about two glasses of buttermilk a day; has plenty of fruit; family of three adults, purchases each month: 100 pounds flour; 1 peck cornmeal, 1 peck potatoes.

Cases 9 and 10.—Mrs. A and son, mill operatives: Breakfast: Bread, coffee, bacon, butter sometimes.

Dinner: Irish potatoes, bulk of meal, bacon and cabbage; cornbread made from shipped meal.

Supper: Cornbread and milk; half gallon of milk used for family of five; no fresh meat.

Case 11.—Mrs. K., inmate of county home. Only case to develop at this home, where she has been an inmate for three years. Breakfast: Grits or rice; biscuit, gravy and coffee; did not eat eggs or meat.

Dinner: Cabbage or beans with one or two Irish potatoes; salt meat usually, but beef or chicken on Sundays, when she ate a fair portion; cornbread; sometimes drank milk for dinner.

Supper: Cornbread and milk; drank one glassful of sweet milk; is particularly fond of cornbread and milk, though she does not drink much milk, rarely more than two glasses a day.

Case 12.—Mrs. McC., wife of mill operative (Newry): Breakfast: Salt pork, biscuits and molasses, butter and coffee; does not eat eggs.

Dinner: Had fresh meat perhaps once a week, but did not eat much; ate a good deal of cornbread with salt pork and cabbage or turnips; perhaps a glass of milk.

Supper: Cornbread and milk, sometimes vegetables left from dinner; had apple pie or cake; no meat.

Case 13.—Mrs. E., wife of mill operative (Newry): Breakfast: Biscuits with butter and syrup or jelly; coffee; eats an egg about once a week.

Dinner: Irish potatoes, sometimes tomato soup (canned tomatoes) and beans; have meat sometimes, but she does not eat it, never did like it; biscuits or cornbread, but she ate biscuits mostly; milk, possibly two glasses; pie often.

Supper: Bread and butter or syrup and milk.

Says she drank about a quart of milk a day. Has had nine children. Disease first noticed just after birth of next to last child.

Case 14.—Mrs. A., wife of mill operative (Newry). Breakfast: Bread and butter or jelly; sometimes eats an egg, but often does not have one for several weeks; says breakfast is usually a biscuit with jelly and coffee.

Dinner: Cornbread with beans or cabbage; does not eat fresh meat; eats more cornbread than anything else, with a glass of milk.

Supper: Cornbread and a glass of milk. Husband works in mill and receives $1 per day. Has two children who go to school. Total income less than $30 a month.

Case 15.—Mrs. W., widow living at Cherokee, farmer. Breakfast: Biscuit, butter and coffee; no meat, no eggs.

Dinner: Cornbread and glass of milk; sweet potatoes often; peas occasionally, other vegetables seldom. Killed one hog last winter, and had fresh pork one week, after that nothing but salt meat.

Supper: Bread and a glass of milk; practically nothing else. Mrs. W. works in the fields herself on this diet.

Such cases might be multiplied indefinitely. A considerable number of other victims of pellagra were seen who lived on such a scanty and one-sided diet. In general, it may be said that the great bulk of the food of these poorer pellagrins consists of wheat flour, cornmeal, potatoes, salt pork and boiled vegetables, and that during the winter even these latter are scarce and consist chiefly of beans and cabbage.

In some instances a considerable amount of canned meats and vegetables were used, but most of the pellagrins did not use these to any extent. It will be seen that the great bulk of the food consisted of carbohydrates and that protein foods such as meat, milk and eggs are relatively little used. It is also important to notice that wheat flour, cornmeal and salt meat are deficient in both scurvy and beriberi vitamins. Potatoes possess the scurvy vitamin, but are relatively very low in beriberi vitamins. It has been demonstrated that the vitamins present in canned goods may be destroyed by the sterilization to which they are subjected. It is therefore clear that these people are living in great part on foodstuffs the continued and disproportionate use of which will produce either beriberi or scurvy, or both. It may be asked why these people do not suffer from these diseases. This is because they all eat sufficient fruit or fresh vegetables to protect them from scurvy, while many of them eat peas and beans frequently. These rank as one of the best preventives of beriberi known. But it is quite reasonable to suppose that possibly there is some third deficiency existing in wheat flour, cornbread, etc., from which they are not protected by these additions. Generally speaking, and with the exception of meat, which is not used largely by the poor, the diet is much more limited in the winter. If pellagra is a deficiency disease, it is during these winter months that it develops and the symptoms appear in the spring. At about that time eggs, milk, fresh vegetables and fruits become abundant and cheap, are used in considerable quantities as compared with the winter diet, and the patients for the most part recover, only to develop another recurrence the following spring after another winter on a comparatively limited diet. It is clear that such observations, while exceedingly suggestive, would not prove the case for deficiency, particularly as sanitary conditions, contacts, etc., were not studied in these cases. It was very desirable, however, to see if this theory could be readily disproven.

Accordingly the diets were investigated in a number of well-to-do cases, for the dietary enthusiast is at once asked the question, How do you explain the cases occuring in well-to-do or even wealthy families, the members of which eat the best of everything? As many of these cases as possible were investigated, but their number is necessarily small. All were in good circumstances, having a sufficient salary and living in good sanitary surroundings with a water carriage system of sewer disposal. No attempt, however, was made to rule out contact with other cases, although in some cases such contact was denied.

Case 1.—Mr. T., a well-to-do farmer, owning his own farm. Breakfast: Hominy, biscuits, butter, molasses and coffee; same the year round.

Dinner: Salt pork with vegetables; usually cabbage or turnips in winter, sometimes peas or beans; sweet potatoes from August to January; Irish potatoes, biscuits and cornbread.

Supper: What remained from dinner with cornbread; drank about a quart of buttermilk a day; seldom ate eggs, and had a chicken about once a week; had fresh pork occasionally in the winter at hog killing time.

This family of seven, with five children, purchased monthly: 75 to 100 pounds of flour, 1½ bushels of cornmeal, sugar and coffee.

Case 2.—Mrs. T., wife of the man in Case 1. Ate exactly the same as above, except that she had steak about once a week for breakfast and ham several days a week for breakfast; ate an egg about twice a week. Dinner and supper the same except that she ate more Irish potatoes than Mr. T.

Case 3.—Mrs. B., wife of mill foreman. Breakfast: Biscuits, butter and coffee; also has either eggs, chicken or fresh beef every day; is not a large eater, however; jelly or preserves.

Dinner: Salt pork with beans or cabbage, Irish potatoes; during summer has plenty of vegetables, but all winter only beans and cabbage; cornbread; milk sometimes during summer, but never in winter.

Supper: Same as dinner. For the four in the family, including two children, they purchase monthly: 50 pounds of flour, 2 pecks cornmeal, 2 pecks potatoes.

Case 4.—Mr. P., government employee. Breakfast: Hominy, a considerable amount; ham and steak were always served, but he liked ham best and would eat that and afterwards perhaps a small piece of steak; bread, biscuits and coffee; ate from four to five biscuits every morning; pancakes and syrup often; coffee.

Dinner: Salt meat with beans, cabbage or turnips, a couple of good sized pieces of cornbread, pie or cake; seldom ate fresh meat for dinner.

Supper: Hash, cornbread and butter, also bakers' bread; ate plenty of cornbread and sometimes ate some cold vegetables.

Case 5.—Mrs. A., sister of physician who lived with her, history obtained from Dr. A. Breakfast: Occasionally fruit and occasionally hominy; did not care much for cereals; bacon and an egg regularly, except when varied with a piece of steak or chicken; biscuits, butter and coffee; hot cakes and syrup frequently.

Dinner: Fresh meat or chicken nearly every day; Irish potatoes and a few vegetables; pie and cake, fruit; cornbread.

Supper: Cold meat, bread and preserves; stated that she was fond of bread and syrup; did not drink milk, did not care for it; stated that she was a fairly hearty meat-eater. However, there were four adults in the family, and a two-pound roast was sufficient for all for one day and sometimes part of the next Used about a dozen eggs a week through the year.

In December she had a baby and nursed it until middle of April, when she was taken sick. Child at birth weighed 10 pounds and weighed 17 pounds when she was taken sick. Lost 20 pounds from December 10 until date of first illness. She has never been in contact with a case of pellagra so far as known.

Case 6.—Mrs. D., housewife in comfortable circumstances. Breakfast: Grits or oatmeal, ham or bacon; eats an egg about two mornings a week; bread, biscuit and postum. States that the chief part of her breakfast is bread and butter and postum.

Dinner: Soup (canned), beans and Irish potatoes; cabbage, corn and other vegetables in summer, but all winter main part of dinner is beans and potatoes; bread and often pie or cake; one glass buttermilk.

Supper: Same as dinner.

Meat is served often, but patient states that she does not care for it and almost never eats it. Three adults in family purchase monthly: 100 pounds flour, 1 peck cornmeal, 1 peck potatoes.

Case 7.—Mrs. B., wife of hardware dealer in comfortable circumstances. Breakfast: Hominy and other cereal; one egg nearly every morning; biscuits or toast, or batter cakes with coffee; very rarely a small piece of steak.

Dinner: Macaroni occasionally, usually Irish potatoes or rice; steak is served for the rest of the family, but she never eats it. States that she never has cared for meat. Occasionally had chicken or fish and might eat a little of these. Practically no vegetables in the winter, when she ate almost nothing but potatoes and bread. Even during the summer, when vegetables were plenty, she ate mostly potatoes, as she preferred them. Has also been a hearty bread-eater, and eats more of this than anything else. Says she could almost live on bread.

Supper: Just bread and jelly. Has eaten this for supper as long as she can remember. Did not drink milk, and used very little butter. Has continued cutting one thing after another out of her diet because she thought they caused indigestion, and for nearly a year before her illness, lived chiefly on bread and potatoes.

Case 8.—Mrs. H., wife of well-to-do public accountant. Breakfast: Hominy with butter; hot bread and tea; during certain times of the year she ate an egg several times a week.

Dinner: Sweet potatoes or macaroni; occasionally ate a very little roast beef; several biscuits; vegetables during summer, but few in winter.

Supper: Bread and grits, tea or cocoa.

Drank very little milk, and ate almost no meat, but was a heavy bread-eater. Says she could have anything she wanted, but simply did not care for meat, eggs or milk.

It is interesting to note that the physician who treated these cases recognized the one sided nature of the diet, and placed both of these patients on a diet practically free from carbohydrates, and in each case the symptoms began to improve promptly after the change of diet.

Case 9.—Mrs. T., housewife in well-to-do circumstances. Breakfast: Either oatmeal or grits; bacon or ham; usually ate an egg several times a week; bread, butter and coffee.

Dinner: Usually salt pork boiled with vegetables. During the winter when there were not many fresh vegetables, used canned goods. Also had canned salmon and salt fish. She served fresh beef several times a week, but she did not care for it and seldom ate it. Ate a small piece of chicken several times a week. She always had boiled rice and also Irish potatoes and ate freely of both, and also of bread. Usually had cake and stewed fruit for dessert.

Supper: Hominy with either cheese, ham or bacon, and rarely eggs. She ate a fair amount of hominy and a considerable amount of bread. States that she is a little inclined to be a vegetarian because she does not like to have animals killed. Drank no milk, ate very few eggs, and bought a large amount of canned goods.

Case 10.—Mr. S., a freight conductor. A very large and muscular man weighing 245 pounds and apparently one of the best nourished men I have ever seen. Eruption of pellagra pronounced, but no other symptoms except that he lost fifteen pounds weight just prior to the appearance of the erythema.

Breakfast: Gets a very early start and usually eats no breakfast. When he does it consists of coffee and a biscuit.

Dinner: Almost always eats Irish potatoes fried with onions, and eats more of these than anything else; cabbage often. Does not eat meat because he does not care for it. Says he does not eat a pound of meat in six months. Has eggs perhaps once a week; beans occasionally; bread; ice cream often.

Supper: Potatoes and onions again whenever he can get them; oysters or fish occasionally, otherwise sandwiches or pie.

Stated that he might drink a glass of milk a day, and never ate butter, but that he was very fond of fresh raw eggs, and when he found some fresh ones, he might eat half a dozen at one meal. Said this did not happen more than

once or at most twice a month. Dietary habits are most erratic, as he is on the road and has to pick up what he can get a good deal of the time, but almost always orders potatoes and onions, for which he has an especial predilection.

A few other cases were seen, all of which were similar to the above. In practically every case there was some peculiarity of taste or a history of indigestion or some other circumstance as a result of which the patient had lived on a very one-sided diet, in every case consisting chiefly of flour, or corn products or potatoes, and often with the addition of salt pork in some form or of canned vegetables. Practically the only case seen in which no obvious flaw could be picked in the diet was Case 5, Mrs. A., who was the sister of a physician. In this case the patient was not seen, but the diet was obtained from her brother. But it is noteworthy that this case occurred immediately following pregnancy and a lactation, in the course of which the patient lost twenty pounds. It can hardly be asserted in view of the loss of about one sixth of the total body weight that the patient was properly nourished, even though no obvious fault can be found with her diet. Pellagra occurs very commonly in women after childbirth. The same phenomenon is seen very often in beriberi, and we may assume that if pellagra is a deficiency disease many women who are receiving sufficient vitamins in their diet to preserve them in health under ordinary circumstances succumb under the additional stress of childbearing. There is no race suicide in this part of the country, and it is quite usual to find from five to eight children in a family.

In this connection it is interesting to note that the commission finds that the incidence of pellagra is highest in women between 20 and 40 years of age; in other words during the childbearing period. The ratio between the incidence rate for female and male in each age period is as follows:

Age.....	0 to 4	5 to 9	10 to 14	15 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69
Female.....	1.1	1	0.7	..	10.8	22.1	3.5	0.5	0.4
Male.....	1.	1	1.	1.	1.	1.	1.	1.	1.

From this it will be seen that as compared with males, the incidence rate of pellagra is practically the same at all age periods for male and female except during the years of sexual activity and childbearing, when the rate is from ten to twenty times higher in women than in men. This peculiarity in distribution is readily explainable according to the dietary hypothesis, and very difficult of explanation if the disease be assumed to be an infection, and such evidence tends to make me favor the dietary deficiency hypothesis.

A number of mill villages were investigated with a view to determining whether any conclusive evidence could be obtained showing that the incidence of pellagra is directly due to the character of the

diet, that is, was more prevalent where the dietary habits were poor and less prevalent where the dietary was better, other conditions remaining the same.

Inasmuch as no conclusive evidence on this point was obtained, the discussion of the results will be much condensed. In general it was found that in those villages in which there was little pellagra, the dietary habits of the people were distinctly above the average of mill villages taken as a whole, but that the lack of pellagra could not logically be attributed to this factor alone, because in such villages the general sanitary conditions were also as a rule distinctly above the average.

The village of Newry will serve as an illustration of this point. Newry is a mill village about five miles from the town of Seneca, S. C., having a population of about 600. Cases of pellagra have moved into this village from time to time, but the disease has not spread, and there has been but one undoubted case of pellagra originating in that village.

The diet of the operatives in Newry is undoubtedly distinctly above the average of other mill villages, and the following points of superiority may be noted:

1. Fresh meat is sold all through the year. I was informed that during June, July and August, 400 pounds of fresh beef was sold weekly together with about 120 pounds of fresh fish. Many fish are also caught in a neighboring stream. Mutton is also sold during the summer, about 1,000 pounds being sold in a season. This is a distinct point of difference from most of these villages, in which no attempt is usually made to sell fresh meat during the summer. During the winter also the per capita consumption of fresh meat, fish, oysters, etc., is above that of the average mill village.

2. The manager of the village store, where practically everything consumed in the town is purchased, has made every effort to handle only the best lines of food products. Thus western cornmeal used to be sold entirely. As a result of the agitation against inferior cornmeal, however, for the past two years the best grade of western corn has been purchased and is now ground at home once or twice a week as desired. The very best quality of meal from the whole corn is therefore the only cornmeal sold at this store. The same care has been observed with regard to other food products.

3. The people of this village as a whole are economically superior to the mill villages as a whole. As a result of methods of administration, there is a very small floating population. Most of the operatives are old residents and 90 per cent. of them are in receipt of wages that may fairly be called comfortable. It may be assumed, therefore, that

in general, such people are better fed than are the operatives in villages where the per capita purchasing power is less, and where general intelligence and efficiency are distinctly less.

4. It should be noted that the only case of pellagra known to have developed in Newry was an exception to this rule, in that a family of four was supported on a wage of $30 a month, and the diet was markedly one sided and monotonous (see Case 14, Mrs. A). The same criticisms may be made of the diets of all of the individuals who were consulted who suffered from pellagra at the time of moving into Newry.

5. In spite of the suggestive nature of this evidence, which points towards dietary deficiency, it is not conclusive because this village had from the time it was built an excellent system of water carriage disposal of wastes. This is an important exception to the average mill village, the great majority of which are provided with open privies of a more or less insanitary type. The adherent to the infection theory may therefore point to this fact as an explanation of the immunity from pellagra enjoyed by Newry.

The answer to this will probably be furnished as the result of the experience of Spartan mills, Spartanburg, S. C. Ever since pellagra has been under investigation at Spartanburg, the operatives of this mill have suffered from a very high incidence of the disease. Their diet has been that of the mill village population in general, and they have always had open privies. In the fall of 1913, however, the installation of a water carriage sewage system was commenced, and by May, 1914, toilet facilities had been finished in every house rented to operatives. The diet has remained unchanged so far as known. If pellagra fails to disappear or to be markedly reduced in amount, this will necessarily discredit the importance of proper sewage disposal as the explanation of the lack of pellagra at Newry.

It would perhaps be unfair to point to the amount of pellagra in Spartan mills this year as an evidence of failure of this sewer system to prevent the disease, since the system has only been in full operation since May of this year. It should, however, be most instructive to compare the future incidence of pellagra in this mill as compared with the incidence prior to the installation of the sewer system.

Evidence obtained at Saxon mills, Spartanburg, while not at all conclusive, in my opinion points toward dietary deficiency. In 1910 there were about 800 operatives in this mill, and the number has remained about constant since that time. In 1911 there was a very considerable increase in the amount of pellagra among these operatives, but in no year since that time has there been any very great number of cases originating. In 1910 the mills were shut down at intervals, so that beginning from July 15 they ran every other week

during the remainder of July and August. They then ran all through September and again shut down the first week in October. They have never shut down since that time. This unemployment, and the resulting shortage in per capita purchasing power may have had some influence in the diets of those who developed pellagra in the winter of 1911. This influence must have been slight, however, and there were probably other, at present unknown, factors operating which assisted in producing the epidemic in 1911. But it is interesting to note that the physician and other authorities at these mills were convinced that the disease was of dietary origin, their theory being that it was caused by bad cornmeal. Thus, prior to 1911 they were using any kind of cornmeal and much of it was bad. They made a change in 1911, and since that time have brought only locally grown corn, which is ground in local mills. The doctor also stated that he had suggested to all his patients that the use of canned goods be discontinued, and that he has endeavored to give instruction on the importance of a more evenly balanced ration, and has, therefore, advocated the use of more meat, eggs, milk, and other protein foods.

The testimony was almost unanimous to the effect that the vegetable gardens had been steadily growing better and better during the last three or four years, except for this last season, when the gardens were all poor, owing to the prolonged dry weather. The people are encouraged to have gardens.

I believe it would be impossible to shake these men from the conviction that pellagra was reduced in incidence as the result of such dietary changes. While of course this is not proof, it appears to me to be significant, especially in view of the fact that no particular sanitary improvements have been made since 1911. They still use the pail system of disposal of excreta. The superintendent of the mill stated that they were always trying to improve the condition of their operatives, and that there had been a gradual improvement in all sanitary arrangements during the last few years, but that no specific sanitary improvement had been undertaken.

I was informed that at Greensboro, N. C., there was a group of mills that were generally speaking markedly superior to the mills already visited in South Carolina, and that the diet of the operatives in particular was very liberal, but that in spite of this fact pellagra had been markedly on the increase there during the past year. These mills were accordingly visited, and the facts were found to be as stated. There are three mills, all under the same management, but having three corresponding mill villages. In all three villages there was an air of prosperity, cleanliness and general well-being far superior to the conditions found in most of the other mill villages seen. The diet in particular was in general excellent. There were several meat mar-

kets in operation the year around, a cold storage plant, and an excellent store. The quantities of meats and other foods sold were investigated and found to be above the average. It may be admitted, therefore, that the diet of these people is, as a general rule, above the average. It was also found that in previous years they had supposed there were not more than four or five cases of pellagra among the total population of these villages, which amounts to about 7,000, but that during this year they had had thirty cases. The managers of these mills, however, are quite benevolently inclined, and this past year have, on their own initiative, employed three trained nurses to visit these employees, care for the sick, and have general supervision over their hygienic surroundings. The head nurse makes periodic reports to the superintendent of all deaths, births and diseases found in these villages. Thus, this year is the first time that any definite information has been obtainable with regard to the diseases in these three mill villages. It seems to me quite possible that the recent increase in pellagra in these villages is therefore only apparent, being caused by the fact that these cases are now being reported, whereas formerly they were unnoticed.

As many as possible of the pellagrins in these villages were visited for the purpose of investigating their dietaries. As in other villages, most of the cases were found to be among the poorer people, but there was a fair number of well-to-do families in which a case of pellagra had occurred. In the great majority of cases, however, the diet of the pellagrin was found to be distinctly monotonous and one sided.

A single instance will suffice here:

Miss F., daughter of a well-to-do mill operative, has had pellagra five years. Breakfast: Biscuits, butter and jelly, coffee; salt meat, a very small quantity several times a week. Family had fresh meat several times a week but she did not care for it. Sometimes ate an egg in the morning. States that for five years she has eaten very little breakfast and sometimes does not eat more than two mouthfuls before she goes to work. She is often not even hungry for her dinner.

Dinner: String beans, or other vegetables, with biscuits or cornbread. In the winter there are few vegetables and she eats beans and Irish potatoes; never eats meat.

Supper: Same as dinner.

Is a hearty bread-eater when she does eat; wheat bread mostly used; drinks no milk; has fruit in summer time.

A comparative study of the diet and general sanitary condition of two institutions was made. The county home at Spartanburg is a charitable institution maintained by the county for its poor and is in reality a large farm. There has been but one undoubted case of pellagra originating on this farm. The inmates live in a little group of cottages in fair sanitary condition. Privies are used except in the hospital. This hospital is a cottage like the others, about 100 yards

from the main group of buildings. It is at present used entirely for poor pellagrins, and a considerable number of cases have been sent there this summer. Although these patients for the most part remain in the hospital, there is no strict segregation practiced, and contact with the other inmates probably has been frequent. All the buildings are unscreened except the hospital, which is partly screened. It was full of flies, however, which could easily pass from the hospital to the kitchen, which was the building nearest to the hospital, or to the other buildings. Yet the disease has not spread among the other inmates of the home.

The diet of the inmates of this home, while not luxurious, is undoubtedly superior to what they had received at their own homes, or to the average diet of the mill village population. Its main points of superiority lie in the fact that the farm has a large herd of cows, as a result of which the supply of milk is practically unlimited, and in the fact that there is a fairly liberal supply of fresh meat. A very large vegetable garden also supplies a sufficiency of all fresh vegetables in season. In general the diet is as follows:

Breakfast: Rice, hominy or oatmeal; bacon or canned salmon; eggs twice a week; bread, butter and molasses; coffee and milk.

Dinner: During the summer, fresh beef or chicken are served on alternate Sundays. During the winter fresh meat is served every day, either beef or pork. Irish potatoes and an ample supply of fresh vegetables are supplied.

Supper: Cornbread, milk and molasses, with the remains of the dinner. A pitcher of milk is always on the table, and all drink as much as they desire. It was stated that many drank two quarts daily.

The Thornwell Orphanage, Clinton, S. C., is a most excellent institution, caring for about 300 orphans. For several years it has been a hotbed of pellagra. The institution has beautiful grounds with substantial stone pavilions, each accommodating a matron and about twenty children from 5 to 18 years of age. There are separate pavilions for boys and girls. Each pavilion has a water closet, but the water supply is insufficient, so that they often cannot be used. At such times open privies are used, and as the children are not very closely supervised, they are distinctly insanitary and much is left to be desired in this respect.

THE TOTAL DAILY DIET FOR 137 CHILDREN

The diet also is very monotonous and one sided. The meals are all cooked at a central kitchen. At the time of our visit there were only 137 children in the home, and the following gives the actual diet of these children as shown on the record book of the kitchen from August 1 to 5 and 10 to 17, the total daily diet for 137 children:

August 1: 5 gallons skimmed milk; 40 pounds flour; 16 pounds lard; beans and corn, amount not stated; 9 cans tomatoes; 4 cans oatmeal—1.5 pound cans; 36 loaves bread.

August 2: 5 gallons skimmed milk; 40 pounds flour; 13 pounds lard; 70 pounds ham; 56 loaves bread; corn; 3 pounds butter; 4 cans oatmeal.

August 3: 5 gallons skimmed milk; 40 pounds flour; 15 pounds lard; beans; corn; 10.5 pounds bacon; 4 cans oatmeal; 36 loaves bread; one-half case fish roe, canned.

August 4: 5 gallons separated milk; 40 pounds flour; 15 pounds lard; 4 cans oatmeal; beans; 15 pounds bacon; corn; 40 loaves bread; 100 pounds rice; 30 eggs; 7.5 pounds sugar.

August 5: 4 gallons separated milk; 31 pounds flour; 10 pounds bacon; 9 pounds rice; 6 pounds lard; 4 cans oatmeal; 3.25 pounds bacon; beans; tomatoes; 36 loaves bread.

August 11: biscuits, oatmeal, beans, eggs boiled, rolls.

August 12: oatmeal, biscuit, corn, soup of 5 pounds bacon, rolls.

August 13: biscuit, three times; oatmeal, beans, beef, rice, rolls.

August 14: biscuit, oatmeal, beef, rice, corn, boiled; rolls.

August 15: biscuit, oatmeal, soup, rolls, tomatoes, raw; figs.

August 16: biscuit, oatmeal, ham, corn, stewed; tomatoes, stewed; rice bread.

August 17: biscuit, oatmeal, corn, stewed; pilau of rice and ham, rolls, ginger bread.

This is a fair sample of the summer diet of the institution. No meat has been served all summer. In the winter they have ham or chicken on Sundays, beef on Wednesdays and Saturdays, and beans on the other days. The supply of fresh vegetables is small in the winter. Syrup is served three times a day and I was informed that the majority of the children eat biscuits and syrup as the main part of the meal.

It is apparent that the main part of the diet of these children consists of wheat flour. The protein constituents are at all times too low, and during the winter, while there is a little more meat, the vegetable supply is markedly reduced. On account of the insanitary condition of the privies it is not possible to incriminate the diet alone as the cause of the incidence of pellagra in this institution, but it seems to me that this obvious defect may very well be the cause.

It may be said, however, that these two institutions afford some evidence in favor of the dietary deficiency hypothesis, and no evidence that disproves this theory. This is the end-result of all of the observations, and we may therefore conclude that no evidence has been found that directly disproves the dietary deficiency theory, but that, on the other hand, there are a number of points in these observations that tend to confirm this theory.

CHANGES OCCURRING DURING THE LAST TEN YEARS THAT MAY ACCOUNT FOR THE INCREASE IN PELLAGRA

It is undoubtedly true that pellagra has existed in this country for some time. Physicians who have been many years in practice state that twenty years ago they had cases in their practice that they then diagnosed in various ways, such as intestinal tuberculosis, but that they now know were cases of pellagra. It is possible and even probable that there was considerably more pellagra then than is generally supposed,

since no one was thinking of that disease. Now that attention is focussed on pellagra, many cases are being diagnosed that suffer from the disease in a very mild form, perhaps suffering only from the typical erythema and totally lacking other symptoms. Such cases would undoubtedly have been very generally overlooked twenty years ago. But while it seems possible, therefore, that the recent increase in the incidence of pellagra may to some extent be explained in this way, it is also apparent that it is becoming more common throughout the South from year to year. This may be regarded as an undoubted fact, and if pellagra is due to a dietary deficiency, it is clear that some explanation must be offered to account for the great increase of pellagra in recent years in accordance with this hypothesis. An attempt was accordingly made to discover any facts that would indicate that changes have occurred in the dietary of the population as a whole during the last ten years, and the information obtained may be discussed as follows:

1. Changes in the population itself: Spartanburg county was selected because of the great increase in the amount of pellagra occurring in this county. The total population of Spartanburg County for the last three decades, according to the U. S. Census, was as follows:

1890	55,385
1900	65,560
1910	83,465

The total population of Spartanburg township, which includes the city of Spartanburg, during the same years was as follows:

1890	13,616
1900	23,810
1910	31,354

It will be seen that there has been a great increase in the population of Spartanburg County during the last twenty years, and particularly of Spartanburg Township, which is almost three times as great as in 1890. Such a large increase is quite unusual for the South and shows a marked variation as compared with the total population of the whole of the state of South Carolina, which was as follows for the same years:

1890	1,151,149
1900	1,340,316
1910	1,515,400

The increase over the preceding census was as follows:

1890	155,572
1900	189,167
1910	175,084

The percentage of increase as compared with the percentage of increase of the whole United States is as follows:

	S. C.	U. S.
1890	15.6	25.5
1900	16.4	20.7
1910	13.1	21.0

From these figures it will be seen that the total population of Spartanburg County, and particularly Spartanburg Township, has increased enormously as compared with the increase in the population of the whole state, in which the increase was in all years considerably below the rate of increase for the United States as a whole.

This increase is to be attributed to a change in economic conditions. It is during these years that most of the large cotton mills have been established in this country, and the increase is largely attributable to the influx of mill operatives and the increased business produced by these mills. It will thus be seen that economic conditions have been completely changed in this country during the last twenty years. While I have had no time to collect statistics from other parts of the South, it is generally recognized that similar changes have been occurring in many localities, and as a whole, the entire South has turned more largely to industrial, manufacturing and mining operations than was the case twenty years ago. In many places, therefore, communities have changed from agricultural pursuits to industrial pursuits, and experience has shown that it is these industrial workers who are especially prone to develop pellagra. Thus the incidence in the mill villages population of Spartanburg County is 104 per 10,000 against 19 per 10,000 for the remainder of the county. Such changes may reasonably explain a great part of the recent increase in pellagra, and when it is admitted, as I believe is the fact, that the dietary of the mill village population as a whole is distinctly inferior to that of the remainder of the people in the county, the possible relation of diet to the increase in pellagra becomes apparent.

2. Changes in the purchasing power of the population during the last decade is important. It is extremely difficult to obtain any definite information on this point, but the testimony is general that economic conditions are generally better in the South now than they were ten years ago. There has been more money in circulation. The price of crops, and particularly of the cotton crop, has as a general rule steadily increased. The people as a whole are making more money. In the case of the mill operatives themselves, although there has been very little increase in the rate of wages, competition between mills has forced an increase in the efficiency of the workers, so that where a weaver ten years ago possibly tended ten machines, he now tends twenty. Although the price per piece may have remained the same, as he now produces much more cloth, he naturally receives a proportionate increase in wages.

But at the same time the purchase price of most commodities, and particularly of the foodstuffs, has soared. Thus, I was informed by one storekeeper, that ten years ago he sold three pounds of his best steak for 25 cents, whereas now the price of steak is 17½ cents a

pound. In other words, the price of beef here is more than double the price ten years ago. Ten years ago he sold eggs at three dozen for 25 cents; now they are 20 cents a dozen, or almost three times the former price. It is unnecessary to dilate further on this tendency for the prices of food to rise, for it is felt and generally recognized all over the country. It is an open question whether the increase in wages in the South has kept pace with the increased price of food, and it seems quite possible that an increasing portion of the population find it more and more difficult to purchase fresh meat, eggs, vegetables and fruits, and that there is accordingly a tendency for many people to cut down the consumption of these high-priced articles of food and increase the consumption of such staples as cornmeal, hominy and flour.

3. An attempt was made to determine whether such changes could be actually demonstrated. Inquiry as to the consumption of fresh meat was made. I was informed by several physicians who had been in practice many years in Spartanburg County that they were certain that as a general rule less fresh meat is eaten now than was the case ten years ago, this fact of course being due to the great increase in the cost of meat. There is practically no meat shipped into Spartanburg County by the western packers, and even in the city of Spartanburg there are no cold storage facilities. All animals consumed are killed locally and promptly consumed. It is largely because of this fact that so little meat is used in the dietary during the summer. On investigation it was found that almost the entire wholesale meat business in Spartanburg County was controlled by one man, Mr. L. S. Donahoe, who operates a slaughter house on the outskirts of Spartanburg. Mr. Donahoe was accordingly visited and he informed me that he was selling just about the same amount of meat to Spartanburg now as formerly; that his business had increased considerably, but that this increase was due to the fact that he was selling meat in other counties, whereas formerly his business had been confined to Spartanburg County. He assured me that he knew to a beef just how much meat had been furnished every year for the past ten years and that the amount remained practically constant for each year. He also promised to give me the exact figures covering the number of animals slaughtered and sold to Spartanburg County for each year, but repeated requests have failed to elicit these important statistics. However, if Mr. Donahoe's statement is accepted at its face value, it is certain that the per capita consumption of fresh meat is much less now than it was ten years ago, for he is now selling about the same amount of meat to a population of 83,465 that he formerly sold to a population of 65,500, according to the preceding census figures.

As to the consumption of canned goods, on every hand testimony was obtained indicating a constant increase. The firm of Shockley and Bull is probably the largest wholesale dealer in such supplies in Spartanburg, and Mr. Shockley was so obliging as to personally compile the following statistics.

Canned goods sold by Shockley and Bull during the fiscal years, 1909 to 1913:

	Canned Meats, Dozen Cans, 1 lb. Basis	Canned Vegetables, Dozen Cans, 3 lb. Basis	Canned Fruits, Dozen Cans, 2½ lb. Basis
1909	4,060	5,630	822
1910	8,091	4,625	328
1911	9,301	4,312	199
1912	7,687	4,509	540
1913	12,218	7,715	532

Mr. Ashmead Courtenay also very kindly sent me the following figures indicating the sales of canned goods at the company store at Newry, S. C.

	Meat, Dozen Cans	Fish, Dozen Cans	Vegetables, Dozen Cans
1906	276	325	228
1907	469	351	418
1908	244	392	356
1909	121	324	518
1910	160	455	370
1911	307	285	294
1912	247	274	385
1913	332	283	478
1914	404	297	614

Similar figures and statements were obtained from all that were questioned on the subject. The facts appear to be that there has been considerable fluctuation in the amounts of canned goods consumed from year to year. Thus, in a year when the gardens are poor, more canned goods are used. But on the whole, there is a well-defined increase in the amount of canned goods used at present over the amount used ten years ago.

The possible changes in the kind of cornmeal and flour used was also investigated. It was found that changes in the variety and quality of both cornmeal and flour used have been frequent. For many years corn has been under consideration as a cause of pellagra, and it is very common to find that as a result of the occurrence of pellagra certain people have eliminated corn from the diet, or have used a locally ground corn in place of shipped cornmeal. Practically all of this cornmeal, however, is made from the whole corn and is not decorticated. On the other hand, practically all of the flour used is fine white flour that has been deprived of all of the outer coats of the

grain, and must therefore be considered deficient in vitamins. But no evidence was obtained indicating any changes in these staples that could account for the increase in pellagra in recent years.[13] It seems more probable that if pellagra is caused by a dietary deficiency, this deficiency has always existed in the cornmeal and flour used, and that the recent increase in the disease is caused by a relatively increased consumption of these articles, with a relative decrease in the consumption of other and more expensive foods.

While endeavoring to elicit information as to changes in the food habits of the people, I was struck by the large number of cases in which information was volunteered as to the change in the lard used. It appears that ten or fifteen years ago about nine tenths of the lard used was pure leaf lard from the hog. Since that time various firms have marketed cottonseed oil substitutes for lard, or compound lards containing a considerable portion of cottonseed oil mixed with lard. The latter, of course, is considerably cheaper. Thus, one store informed me that in 1907 they sold more pure lard than compound, while now they sell ten times as much compound lard as leaf lard. A few people even hazarded the opinion that pellagra might be due to the use of cottonseed oil. As popular opinion at times incriminates about every article of food used, such opinions are worthless. However, it may be pointed out that we know very little of the food value of cottonseed oil as compared with lard, and it is quite possible that lard may be more readily assimilated and may possess a higher food value than cottonseed oil. Further, such a marked change in the dietary habits of a community is a sufficient refutation of the argument that pellagra can not be of dietary origin, because there has been no change in the food habits of the people. Such changes have occurred. The changes mentioned may or may not be important in the causation of pellagra. But even if these changes are unimportant, the fact that they can be demonstrated opens the possibility that there may be other and more important changes that may have occurred in the food habits of the people during the last decades, and that some of these changes may be connected with the contemporaneous increase in the incidence of pellagra.

In conclusion it may be stated with regard to the foregoing argument that while I have endeavored to avoid making unfair statements or comparisons, I have made no attempt to present arguments in favor of the infection or intoxication hypotheses. The commission requested that I attempt to present the case for the dietary hypothesis as I see

13. Voegtlin, Sullivan and Myers, Pub. Health Rep., April 14, 1916, p. 935, stated that this highly milled wheat flour began to be introduced about 1880. If this statement is correct, the introduction of this foodstuff, proved to be deficient in vitamins, corresponds closely with the increase in pellagra.

it, and I have endeavored to do this, knowing that the presentation of the other side would be left in competent hands. While I am personally inclined to believe that the most probable cause of pellagra is a deficiency in some vitamin, it is evident that this hypothesis has not been scientifically demonstrated, but is still only hypothesis. It is believed, however, that the following conclusions may be drawn from this investigation.

CONCLUSIONS

1. There is a certain similarity between pellagra and other known deficiency diseases, namely, beriberi and scurvy.

2. Much of the evidence that has been presented as a proof of the infectious nature of pellagra can be reasonably explained in accordance with a deficiency hypothesis.

3. A deficiency is demonstrable in the diets of most pellagrins. This deficiency appears to me to result from the too exclusive use of wheat flour, in association with cornmeal, salt meats and canned goods, foods that are known to be deficient in vitamins.

4. Changes in the diet of the people of the South have occurred during the past ten or fifteen years. Since we do not know all the changes that have occurred, and cannot judge accurately the importance of the known changes, it is unscientific to assume that the recent increase in pellagra cannot be due to such changes.

5. The hypothesis that pellagra is caused by a deficiency is very plausible and must be taken into consideration in subsequent studies of this disease.

THE INCIDENCE OF PELLAGRA IN SPARTANBURG COUNTY, S. C., AND THE RELATION OF THE INITIAL ATTACK TO RACE, SEX AND AGE*

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INTRODUCTION

The extensive records accumulated during the field study of pellagra in Spartanburg County, S. C., have presented an opportunity to inquire into the behavior of this disease in a population of considerable size living under natural conditions of civil life. Such an inquiry might be expected to contribute something to the general prognosis of pellagra in the population of the county and in the Southern states as a whole and it might even bring to light some facts of value in the prognosis in an individual case of the disease. Manifestly, also, it is desirable to know fairly well the course of the disease as a biological phenomenon, uninfluenced by intentional drugging, dieting or climatic changes, in order to estimate the possible influence which these latter may exert on the course of pellagra. Fortunately for the purpose of such a study, a considerable proportion of the pellagrins of our series have received no particular treatment directed against the disease; in fact, many had suffered from pellagra for years without the nature of the ailment being recognized. The recorded material is rich in possibilities of analysis. It seems wisest to direct attention to certain specific points, one at a time. Many important facts in regard to these cases will be found recorded and discussed in other papers of this series, constituting our third report, and also in the preceding first and second progress reports of this commission.

In the present paper we purpose to present the recorded facts in respect to incidence of pellagra and its death rate in the year of initial attack in each year since the appearance of the earliest recognized case in the county and the correlations between race, sex and age on the

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* From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.
* The final copy of this paper has been written since Dr. Garrison and Dr. Siler were recalled to active duty in the Medical Corps, U. S. Navy, and the Medical Corps, U. S. Army, respectively. Although they are quite familiar with the general nature of the paper and with the conclusions, they are not personally responsible for the detailed compilation of data or for the specific deductions drawn from them.

one hand, and incidence of pellagra and death rate in initial attack on the other, as shown by the total cases on our records at the end of the field work in 1914. In subsequent papers we purpose to consider the tendency to recurrence, death rate in recurrence and tendency to recovery.

The present paper deals only with incident, or initial attacks, of pellagra and not with recurrences of the disease, a sharp distinction being made between incident, or first attack, and subsequent, or recurrent attack, of the disease.

INCIDENCE OF PELLAGRA IN EACH YEAR

In all cases of our series subsequent to 1907, we have arrived at a decision concerning the year in which the first erythema appeared, but we do not wish to maintain that these decisions are in every case correct. For those cases originating previous to 1908 it has not been possible to arrive at a decision in all instances. Of the 1,180 recognized pellagrins on our records at the end of 1914, there are fifty-seven cases in which the initial erythema appeared before 1908. The available evidence indicates with considerable certainty that the initial attacks appeared in these patients in the different years as shown in Table 1.

TABLE 1.—DISTRIBUTION OF CASES OF PELLAGRA INCIDENT BEFORE 1908, ACCORDING TO YEAR OF ONSET OF THE FIRST ERYTHEMA

Year	1888	1889	1890	1891	1892	1893	1894	1895	1896	1897	1898	1899	1900	1901	1902	1903	1904	1905	1906	1907	Uncertain	Total
Patients	1	0	0	0	1	1	2	0	0	0	1	0	3	3	2	6	5	10	6	14	2	57

Concerning those pellagrins who suffered their first attack in 1908, 1909, 1910 or 1911, we have somewhat more reliable information, because during these years the physicians of the county were already acquainted with the disease, but it is still probable that the list of cases is very far from complete, more particularly in the earlier years. The recorded statistics for 1912, 1913 and 1914, and probably also for 1911, are distinctly more reliable and complete and probably approach very nearly the degree of accuracy attainable in field work of this sort, because of our presence in the field during 1912, 1913 and 1914. We are inclined to regard the recorded statistics for 1912 as somewhat more complete than those for 1914, because the observations made in 1912 have been added to by further observations during two subsequent years. The incidence of pellagra in each year subsequent to 1907 is shown in Table 2 and the data are presented graphically in Figure 1.

TABLE 2.—DISTRIBUTION OF TOTAL RECORDED PELLAGRINS ACCORDING TO YEAR OF ONSET OF FIRST ERYTHEMA

Year	Before 1908	1908	1909	1910	1911	1912	1913	1914	Total
Patients	57	20	57	141	234	211	251	209	1,180

The recorded data indicate that the number of new cases each year has increased rapidly from 1908 to 1911, and that the incidence rate has changed but little from 1911 to 1914. These indications may be questioned to some extent. We are inclined to accept the indication of an actual rapid increase from 1908 to 1911 in the number of individuals newly attacked by pellagra, but we think that the magnitude

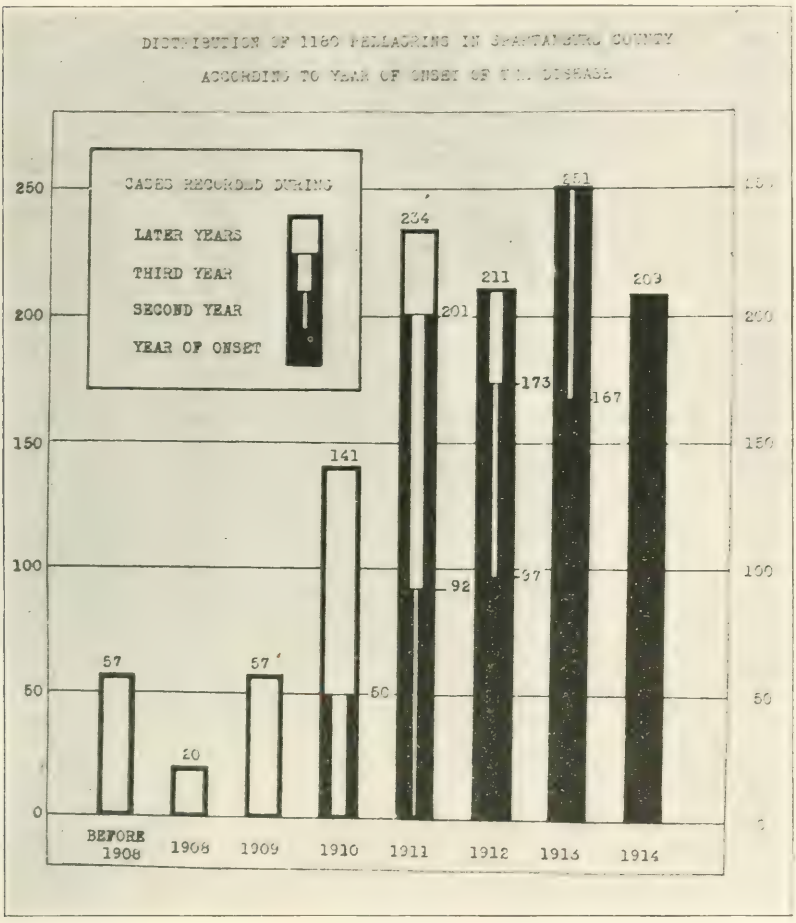

Fig. 1.—The total height of each column indicates the total number of new cases of pellagra in the respective year, according to our records at the end of 1914. The height of the solid black column indicates the number of new cases recognized and recorded by us during the year in which the disease began. For 1914 the whole column is, of course, solid black.

of this increase is somewhat exaggerated in the table because of relatively incomplete records for the earlier years. In other words, we are actually convinced that there were very many more new cases of pellagra in Spartanburg County in 1911 than in 1908, probably at least

four times as many, but the indicated elevenfold increase appears too large. In the statistics of cases originating subsequent to 1911 another factor of error assumes prominence. This depends in part on the evident tendency of many pellagrins to conceal their disease until it recurs once or even twice, and in part on the necessary incompleteness of our survey of the county in each year, as a result of which many incident cases, especially those arising later in the season, escaped discovery during the year of the initial attack. Thus, at the end of 1912, our first year in the field, we had recorded only ninety-two cases which originated in 1911; at the end of 1913 this number had been augmented to 201, and at the end of 1914 it had been further increased to a total of 234. In a similar way the number of pellagrins with onset in 1912 who had been recognized and recorded at the end of 1912 was only ninety-seven; in 1913 there were added seventy-six, making 173, and during 1914 there were discovered thirty-eight more pellagrins with onset in 1912, augmenting the total to 211. The number of patients with onset in 1913 recognized and recorded during 1913 was 167, and in 1914 we added eighty-four to this number, making a total of 251 with initial attack in 1913. If, therefore, one should compare the total recorded pellagrins incident in 1914 with the analogous figures for 1912 and 1913, as the figures stood at the end of the field work of the respective years, a very considerable increase in the new cases of pellagra would be indicated, namely, from 97 to 167 to 209 for 1912, 1913 and 1914, respectively. We are not inclined to regard these figures as a true measure of the increase in new cases of the disease in the last few years, for it is doubtless true that the data obtained in 1914 are more complete than those obtained in previous years, because of the greater experience of the observers and more thorough acquaintance with the field of work, but in this connection it should be mentioned that our field work ended on Oct. 15, 1914, and necessarily many portions of the county had not been visited for several weeks previous to that time. Judging from the experience of earlier years, it seems assured that further systematic field work in 1915 and 1916 would bring to light from sixty to eighty additional cases of pellagra which had their onset in 1914.

The year 1911 merits special consideration because of the relatively excessive number of pellagrins recorded as having the initial attack in that year. It is possible that some cases which actually originated earlier have been placed in 1911, because of the widely awakened interest in pellagra in Spartanburg County during this year. Dr. R. M. Grimm[1] made an epidemiologic survey of certain portions of this county in 1911, and there can be no doubt but that his presence and the

1. Grimm, R. M.: Pellagra: a Report on Its Epidemiology, U. S. Pub. Health Rep., 1913, xxviii, 427, 491.

stimulus of his work brought to light many cases not previously recognized, although the disease had actually originated earlier in these patients. On the other hand, many physicians who have been practicing in the region for many years have expressed the opinion that 1911 was an exceptional year for pellagra and that a disproportionately large number of new cases actually did arise in that year, not only in many parts of Spartanburg County, but also in neighboring counties. This opinion possesses some weight and lends support to the indication of high incidence in 1911 shown by the recorded statistics.

From a consideration of these various sides of the question, we have arrived at the conclusion that the number of new cases of pellagra in Spartanburg County has been increasing somewhat, probably about 10 per cent. per year on the average, during the last three or four years, and that the increase previous to 1911 was at a more rapid rate.

DEATHS DURING THE YEAR OF INITIAL ATTACK

For the purpose of this study we have arbitrarily decided to consider a death which occurred previous to February 1 of the year following the initial erythema as a death in the first attack of pellagra. In many instances it has been impossible for us to estimate the relative importance as a cause of death of the pellagra as compared with other diseases from which the patient may have been suffering, and therefore unless it has been perfectly clear that death resulted without relation to pellagra the death has been included as due to this disease.

Of the total 1,180 recorded pellagrins, 187 died during the year of initial attack, as defined in the preceding paragraph, indicating a death rate in the first attack amounting to 15.8 per cent. This figure is undoubtedly too high rather than too low, because in pellagra, as for vital statistics in general, mortality reports tend to be more complete than morbidity reports, however much care be devoted to the matter. Doubtless, also, some of these deaths occurred during a year subsequent to that of the initial erythema, the latter having escaped observation and record.

The deaths in initial attack include, as previously stated, those deaths which occurred up to February 1 following the year of initial erythema, in addition to those which occurred in the respective year. Their distribution by years is shown in Table 3.

TABLE 3.—Distribution of Deaths in Initial Attack of Pellagra According to Year of Onset of the Initial Erythema

Year	Before 1908	1908	1909	1910	1911	1912	1913	1914	Total
Incident cases	57	20	57	141	234	211	251	209	1,180
Deaths	13	2	16	28	33	27	38	30	187
Death rate, per cent.	22.8	10.0	28.1	19.9	14.1	12.8	15.1	14.4	15.8

The gross indicated death rate, 15.8 per cent., is after all not so very much greater than the rate calculated for each of the last four years. One may conclude, therefore, that the death rate for pellagra in Spartanburg County has been between 10 and 16 per cent., and that there is no conclusive evidence that this death rate has increased or diminished progressively during the past four years. Previous to 1911 the death rate indicated by the records was considerably higher, but this indication should not be too readily accepted without some thought of the incompleteness of the data. It is not improbable that an appreciable number of those who died of pellagra in 1909 and 1910 may actually have had an unrecorded initial erythema in some previous year, so that they really died in a recurrence rather than in the first year of the disease.

RELATION OF PELLAGRA INCIDENCE TO RACE, SEX AND AGE

The important relations of age and sex to pellagra, as well as the racial distribution of the disease, have been discussed in our previous reports, more completely in the second progress report.[2] It is our purpose to consider these relationships in greater detail in the much larger group of cases now available.

Of the total 1,180 recorded pellagrins, 1,026 were white and 153 were colored (including mixed blood), giving a ratio of 6.7 to 1. This agrees well with the ratio shown in the previous report, cited above, upon the 780 cases recorded to the end of 1913, of which 680 were white and 100 colored, giving a ratio of 6.8 to 1. The number of white persons and colored persons who suffered an initial attack of pellagra in each year subsequent to 1907 is indicated in Table 4. According to the available records the proportion of negro pellagrins was relatively less some years ago and has been increasing somewhat since 1911. Of the 509 recorded initial attacks up to the end of 1911, there were fifty-three, or 10.4 per cent., in colored persons, whereas, of the 671 cases originating since the end of 1911, no less than 100, or 14.9 per cent., have been in the colored race.

TABLE 4.—WHITE AND COLORED PELLAGRINS DISTRIBUTED ACCORDING TO THE YEAR OF INITIAL ERYTHEMA

Year	Before 1908	1908	1909	1910	1911	1912	1913	1914	Total
White	51	20	53	123	209	182	213	176	1,027
Colored	6	0	4	18	25	29	38	33	153
Total	57	20	57	141	234	211	251	209	1,180
White, per cent.	89.5	100.0	93.0	87.2	89.3	86.3	84.9	84.2	87.0
Colored, per cent.	10.5	0.0	7.0	12.8	10.7	13.7	15.1	15.8	13.0

2. Siler, Garrison and MacNeal: Statistics of Pellagra in Spartanburg County, S. C., THE ARCHIVES INT. MED., 1915, xv, 98; Second Progress Report, 1915, 121.

In our previous report it has been pointed out that the white population of Spartanburg County is about twice as numerous as the colored population, 57,048 and 26,410, respectively, according to the U. S. Census, 1910, so that the pellagra morbidity among negroes was only about one third of the morbidity rate for the white population. As we have previously stated, we regard this disparity not as evidence of racial resistance to pellagra on the part of negroes, but as a result of their different living conditions and partial social segregation from the inhabitants of the endemic foci of the disease. It now appears that this disparity is showing a slight tendency to become equalized, but that the negro race still remains very much less afflicted with pellagra than the white race in Spartanburg County. The gradual relative increase of pellagra in the colored race in this county might be expected as the disease gradually extends more and more from its principal endemic foci in the mill villages out into the rural population.

The relationship between race and death rate from pellagra clearly indicates lesser resistance in the negro race, once the disease has been contracted. Of the 1,027 white pellagrins, 123, or 12 per cent., died in the year of the initial erythema (including the following January), whereas, of the 153 negro pellagrins, no less than sixty-four, or 41.8 per cent., died during the year of the initial erythema. In short, pellagra in Spartanburg County attacks members of the negro race less frequently, but it is far more fatal to them when they are attacked, a condition of affairs which finds analogy in many other diseases due to infection.

The high death rate in pellagra among negroes in the United States has been repeatedly observed. Searcy's early report[3] indicated a high death rate among negroes in a hospital for the insane, namely, 64 per cent. Lavinder[4] has published the statistics of reported cases and reported deaths in Mississippi from January to June, 1913. The ratio between number of reported deaths and number of reported cases in the white race was 74 to 648, or 11.4 per cent., and the analogous ratio for the negro race was 194 to 665, or 29.2 per cent.

The relationship between age and sex and the incidence of pellagra has been discussed in our previous reports. In the series of 1,180 cases now available, the relationships are similar in character to those previously found, but the larger number of cases now warrants the consideration of these questions in somewhat greater detail. In the present study each case has been tabulated according to age at onset of the initial erythema and the data are shown in Table 5. The distribution.

3. Searcy, George H.: An Epidemic of Acute Pellagra, Jour. Am. Med. Assn., 1907, xlix, 37.

4. Lavinder, C. H.: Pellagra in Mississippi, U. S. Pub. Health Rep., 1913, xxviii, 2035.

TABLE 5.—Distribution of Pellagrins According to Race, Sex and Age at Onset of First Erythema

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0	1	2	3	0	0	0	1	2	3
1	4	6	10	0	1	1	4	7	11
2	7	12	20*	0	0	0	7	12	20*
3	12	8	20	0	0	0	12	8	20
4	17	14	31	0	1	1	17	15	32
5	6	8	14	0	1	1	6	9	15
6	11	19	30	1	0	1	12	19	31
7	11	9	20	0	1	1	11	10	21
8	9	5	14	0	0	0	9	5	14
9	10	8	18	1	2	3	11	10	21
10	7	8	15	0	0	0	7	8	15
11	4	5	9	0	0	0	4	5	9
12	2	2	4	0	0	0	2	2	4
13	4	1	5	0	0	0	4	1	5
14	1	6	7	0	0	0	1	6	7
15	2	2	4	1	0	1	3	2	5
16	8	0	8	3	0	3	11	0	11
17	12	3	15	3	1	4	15	4	19
18	13	2	15	5	1	6	18	3	21
19	12	1	13	4	0	4	16	1	17
20	15	0	15	1	0	1	16	0	16
21	20	3	23	5	2	7	25	5	30
22	23	4	27	6	2	8	29	6	35
23	25	2	27	8	0	8	33	2	35
24	23	1	24	7	0	7	30	1	31
25	31	5	36	6	1	7	37	6	43
26	26	3	29	2	0	2	28	3	31
27	20	1	21	2	0	2	22	1	23
28	14	3	17	2	1	3	16	4	20
29	20	2	22	3	0	3	23	2	25
30	22	1	23	9	1	10	31	2	33
31	19	1	20	2	0	2	21	1	22
32	19	6	25	3	0	3	22	6	28
33	20	3	23	3	1	4	23	4	27
34	22	6	28	4	0	4	26	6	32
35	22	4	26	2	1	3	24	5	29
36	14	7	21	4	1	5	18	8	26
37	15	9	24	1	1	2	16	10	26
38	9	1	10	0	1	1	9	2	11
39	12	2	14	2	0	2	14	2	16
40	14	7	21	2	0	2	16	7	23
41	7	3	10	1	0	1	8	3	11
42	18	5	23	1	0	1	19	5	24
43	7	4	11	0	0	0	7	4	11
44	12	6	18	1	0	1	13	6	19
45	6	4	10	2	1	3	8	5	13
46	9	3	12	2	0	2	11	3	14
47	4	4	8	0	0	0	4	4	8
48	5	3	8	0	1	1	5	4	9
49	5	5	10	2	0	2	7	5	12
50	7	4	11	3	3	6	10	7	17
51	7	4	11	0	0	0	7	4	11
52	1	5	6	0	1	1	1	6	7
53	7	3	10	3	0	3	10	3	13
54	4	8	12	0	0	0	4	8	12
55	4	8	12	1	0	1	5	8	13
56	6	4	10	1	0	1	7	4	11
57	1	4	5	1	2	3	2	6	8
58	4	5	9	0	0	0	4	5	9
59	3	4	7	1	0	1	4	4	8

* Including one white child, aged 2, sex unknown.

TABLE 5.—Distribution of Pellagrins According to Race, Sex and Age at Onset of First Erythema—(*Continued*)

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
60	5	1	6	0	4	4	5	5	10
61	2	2	4	0	0	0	2	2	4
62	2	5	7	0	0	0	2	5	7
63	4	2	6	1	0	1	5	2	7
64	2	7	9	0	0	0	2	7	9
65	3	1	4	0	0	0	3	1	4
66	2	0	2	0	0	0	2	0	2
67	0	1	1	0	2	2	0	3	3
68	0	3	3	2	1	3	2	4	6
69	1	1	2	0	0	0	1	1	2
70	2	2	4	0	0	0	2	2	4
71	0	0	0	0	0	0	0	0	0
72	0	1	1	0	0	0	0	1	1
73	0	2	2	0	0	0	0	2	2
74	0	1	1	0	0	0	0	1	1
75	0	1	1	0	0	0	0	1	1
76	0	0	0	0	0	0	0	0	0
77	1	0	1	0	0	0	1	0	1
78	0	1	1	0	0	0	0	1	1
79	0	0	0	0	0	0	0	0	0
80	0	0	0	0	1	1	0	1	1
81	0	0	0	0	0	0	0	0	0
82	0	1	1	0	0	0	0	1	1
83	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0
85	0	0	0	1	0	1	1	0	1
86	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0
Total, age known	689	310	1,010*	115	36	151	814	346	1,161*
Age unknown	13	4	17	2	0	2	15	4	19
Total	**712**	**314**	**1,027***	**117**	**36**	**153**	**829**	**350**	**1,180***

* Including one white child, aged 2, sex unknown.

according to age at the time of onset, of the total 1,180 pellagrins is shown graphically in Figure 2; of the 712 white females in Figure 3; of the 314 white males in Figure 4, and of the 117 colored females and thirty-six colored males in Figure 5.

One important point brought out here is the occurrence of fourteen initial attacks of pellagra before the age of two years, three of them in the first year of life and eleven in the second. These fourteen cases amount to more than 1 per cent. of the total 1,180 cases, a proportion somewhat greater than that shown in the previous study[5] of 253 pellagrins according to age at onset of the disease, in which series there were only two individuals under the age of two years.

5. Siler, Garrison and MacNeal: The Archives Int. Med., 1915, xv, 106: Second Progress Report, 1915, 121.

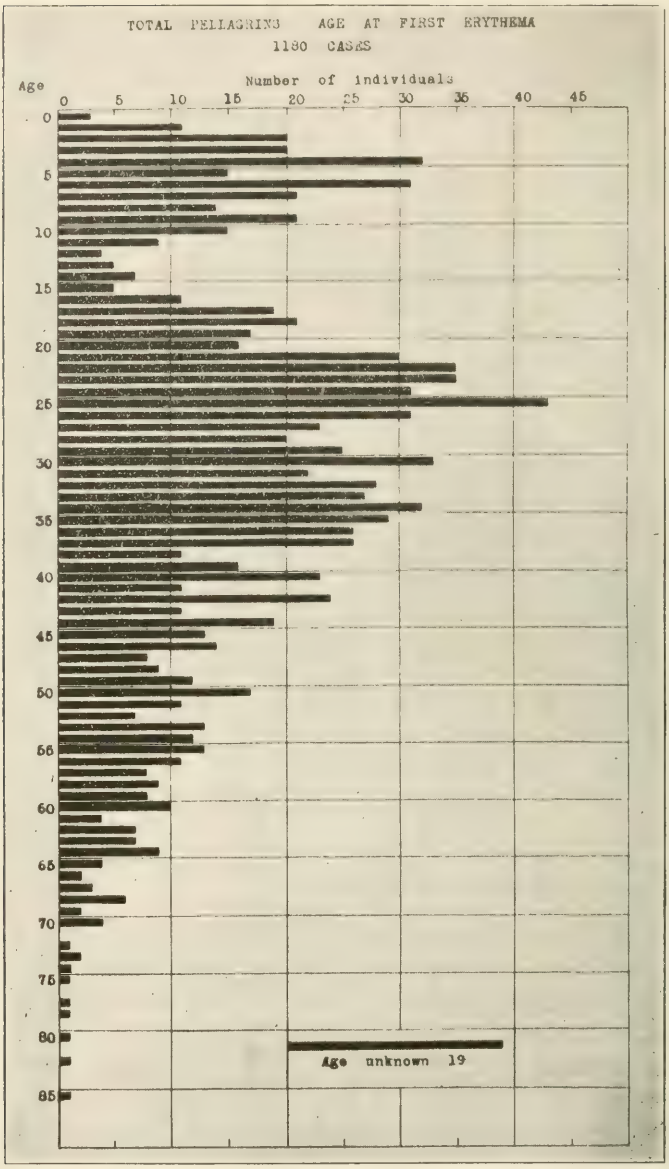

Fig. 2.—The distribution, according to age in years at the onset of the initial erythema, is shown for 1,161 pellagrins. In nineteen cases the age at onset could not be ascertained. One white child, aged 2, whose sex was not recorded, is also included here.

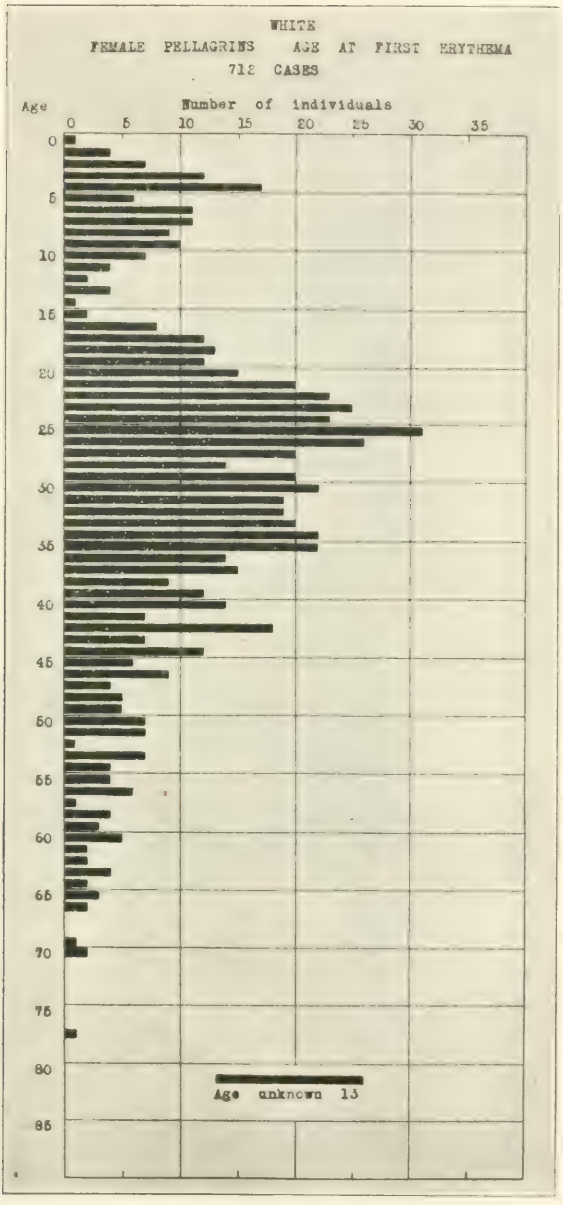

Fig. 3.—The distribution, according to age in years at the onset of the initial erythema, is shown for 699 white female pellagrins. In thirteen cases the age at onset could not be ascertained.

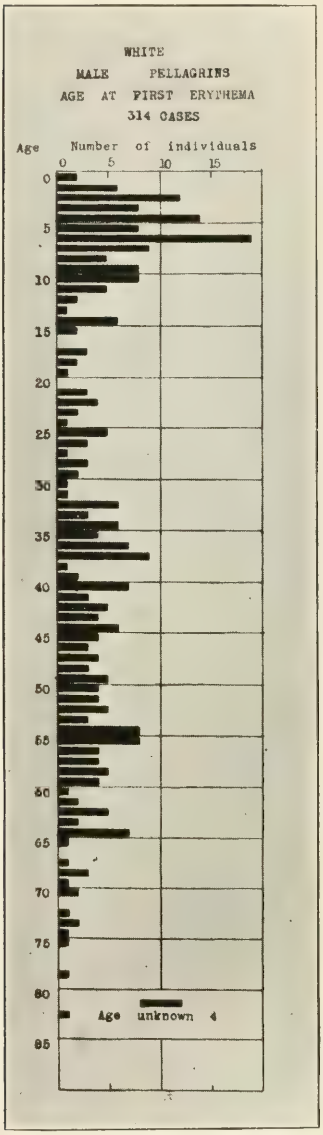

Fig. 4.—The distribution, according to age in years at the onset of the initial erythema, is shown for 310 white male pellagrins. In four cases the age at onset could not be ascertained.

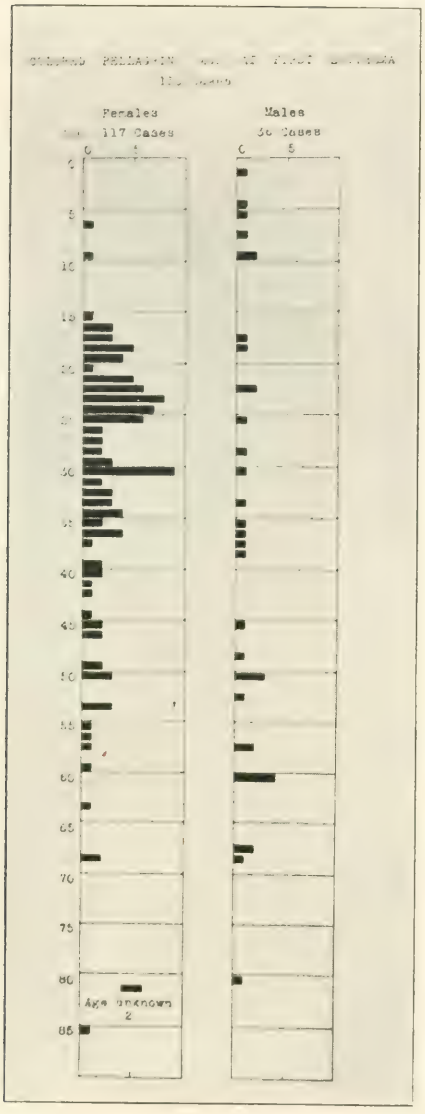

Fig. 5.—The distribution, according to age in years at the onset of the initial erythema, is shown for 115 colored female pellagrins and thirty-six colored male pellagrins. In two of the colored female pellagrins the age at onset could not be ascertained.

These fourteen cases, which originated before the age of two years, are perhaps worthy of a detailed consideration.

Pellagrin 120: I. L., girl, was born in October, 1909. The initial attack of pellagra began June 1, 1911, at the age of 19 months, with recovery. She had measles in January, 1912, and died of dysentery after a week's illness in April, 1912. Whether this dysentery was or was not a manifestation of pellagra is uncertain. There was no pellagra in any other member of the family. An adult pellagrin, No. 353, residing next door, suffered a severe recurrent attack of pellagra, lasting all summer, in 1911, and died of it in November, 1911. An unrelated woman, Pellagrin 678, living in the same house with the child, Pellagrin 120, suffered an initial attack of pellagra at about the same time as the child. This case, Pellagrin 120, was reported to us by Dr. A. W. Nelson of Spartanburg and was not seen by any member of our commission.

Pellagrin 173: A. J., boy, was born in March, 1910. The onset of the initial erythema occurred in June, 1911, at the age of 15 months. The case was seen and diagnosed by Dr. J. W. Babcock of Columbia, S. C. There were no recurrences in 1912, 1913 or 1914. This boy's mother, Pellagrin 171, had her initial attack of pellagra in October, 1910, six months after the child's birth, and she had a recurrent attack in April, 1911, two months before the onset of the erythema in the child. These attacks of pellagra were not seen by any member of our commission.

Pellagrin 179: R. L. R., boy, was born June 10, 1910. The initial erythema began in February, 1912, at the age of 20 months, on the backs of the hands and wrists, and it was accompanied by diarrhea. The erythema appeared on the feet in June and this was still desquamating when the patient was seen by us Aug. 23, 1912. The erythema recurred on hands and feet in 1913 and again in 1914 and the little boy died in July, 1914. The older sister of this child, Pellagrin 310, is said by the parents to have had the same disease when she died in August, 1910, at the age of 4 years. A paternal aunt, Pellagrin 170, living in the same house, developed pellagra for the first time in June, 1911, and had a severe recurrence in 1912. In February, 1911, this child, Pellagrin 179, with his parents, moved to another house, next door but one to the former residence, and it was at this new residence that the symptoms of pellagra appeared, in February, 1912.

Pellagrin 184: W. B., colored boy, was born March 4, 1911. The initial attack of pellagra began with erythema and dysentery on June 7, 1912, at the age of 15 months, and terminated in death July 6, 1912. The child had been weaned on May 25, only a short time before the onset of pellagra, but he had been eating an indiscriminate diet since the age of 5 months. The child's mother, Pellagrin 183, developed her initial attack of pellagra June 1, 1912, a few days before the onset of the erythema in his case. A paternal aunt of the child, Pellagrin 67, visited this family during May and June of 1912, and the onset of her cutaneous eruption occurred at their home on May 22, 1912. The disease appeared in her sister-in-law, Pellagrin 183, and nephew, Pellagrin 184, in less than three weeks after the appearance of the erythema in their guest. This child was seen by Dr. J. C. Moore of Duncan, S. C., who made the diagnosis, and the family was interviewed by us in August, 1912, six weeks after the child's death.

Pellagrin 643: L. O. A., girl, was born Aug. 23, 1907. The initial attack of pellagra began in July, 1909, at the age of 22 months, and the disease recurred in the summer of 1910. There was no recurrence in 1911, 1912, 1913 or 1914. The case originated in an endemic focus of pellagra outside of Spartanburg County and moved into this county at a later date. There were no other known pellagrins in the family. The diagnosis of this infantile case rests entirely upon the history.

Pellagrin 645: F. S., boy, was born Sept. 24, 1909. The onset of pellagra occurred, according to the mother, in March, 1910, at the age of 6 months.

The disease recurred in the summer of 1911 and again in 1912, but there was no recurrence in 1913 or 1914. His mother, Pellagrin 644, had her initial attack of pellagra in April, 1909, five months before his birth, and she had mild recurrences in 1910, 1911, 1912 and 1913, but no recurrence in 1914. Her mother, the maternal grandmother of Pellagrin 645, is also a pellagrin, Case 83, with onset in 1910. This family was first seen by us in 1913 and the diagnosis of infantile pellagra rests entirely upon the history.

Pellagrin 672: B. D., boy, was born in the spring or summer of 1910. The onset of pellagra occurred in the summer of 1911, at the approximate age of 1 year. There was no recurrence in 1912, 1913 or 1914. The boy's paternal grandfather, Pellagrin 131, lived in the same household. He had suffered his first attack of pellagra in 1910 and had a severe recurrence early in the spring of 1911, preceding the onset of the disease in the child. The child's father, mother and sister have not shown any signs of the disease. This case occurred before the beginning of our field work and the diagnosis of infantile pellagra rests entirely upon the history.

Pellagrin 888: F. E., boy, was born Aug. 18, 1908. The onset of pellagra occurred, according to the parents, in March, 1909, at the approximate age of 6 months. The disease recurred each spring, 1910, 1911, 1912, 1913 and 1914. There are no other known pellagrins in the family and only a history of visiting at the house of a pellagrin during early infancy. This case came under our observation for the first time in 1914. The patient was seen, however, by Dr. J. J. Allen of Enoree, S. C., in the spring of 1909, and he states that pellagra actually was present at the age of 6 months, evidenced by characteristic erythema of the hands and feet and well-marked gastro-intestinal symptoms.

Pellagrin 1010: D. T., boy, was born Oct. 3, 1912. The initial attack of pellagra began in June, 1914, at the age of 20 months. There were no other known pellagrins in the family. This boy contracted the disease while living in an endemic focus in a neighboring county and came under our observation when the family moved to Spartanburg in June, 1914. The attack of pellagra was very definite and the eruption quite typical. It was still present at our last recorded observation, Aug. 12, 1914.

Pellagrin 941: C. L. C., girl, was born June 23, 1912. Her initial pellagrous erythema began May 1, 1914, at the age of 22 months. She was seen by us on June 14, 1914, when a typical erythema of the backs of the hands was still present. A maternal uncle, Pellagrin 449, came to make his home with this family in August, 1912. He had had an attack of pellagra in 1912 and possibly also in 1911. There was a severe recurrence in March, 1913, and again in May, 1914, resulting in death at the Pellagra Hospital on May 30, 1914. Another maternal uncle of this baby, Pellagrin 856, who had been suffering from gastro-intestinal trouble for three years and had been adjudged insane in 1912, came on a visit to this family in May, 1913. A pellagrous erythema appeared upon his hands early in June, 1913. He left again in July and died of pellagra in North Carolina, Aug. 14, 1913. He probably had had the diagnostic erythema in previous years, but the evidence on this point is not conclusive. The baby's mother, Pellagrin 450, showed her first definite erythema in March or April, 1913, with recovery, and there was no recurrence in 1914. The baby slept with her uncle, Pellagrin 449, up to the time he was taken to the hospital.

Pellagrin 1026: T. L., girl, was born in November, 1912. The initial erythema appeared July 23, 1914, at the age of 20 months. The child's father, Pellagrin 529, developed his initial attack of pellagra on March 17, 1913, at a village about ten miles from Spartanburg. The attack was severe and, as he was unable to support his wife and child, all three were taken into the home of the wife's parents, who, although not in comfortable circumstances, were nevertheless somewhat above the average of mill workers in financial status. Six weeks later, on May 17, 1913, the wife's father, Pellagrin 530, came down with a severe initial attack of pellagra, from which he died on July 16.

1913, at the Pellagra Hospital, four days after admission. At about the same time, his wife, Pellagrin 1228, developed a mild erythema from which she soon recovered. A son of the old man lived just across the street and his wife, who was assisting in her father-in-law's household during this time of sickness, also developed her initial attack of pellagra about May 15, 1913, which proved to be mild in character. The original patient, Pellagrin 529 (patient's father), was sent away to the mountains of Tennessee on June 15, 1913, and he died there shortly afterward. The old lady, Pellagrin 1228, died early in 1914, without recurrence. The baby, Pellagrin 1026, showed her initial erythema in July, 1914, and was evidently recovering when seen by us on Aug. 6, 1914. No other members of the family had shown any evidence of pellagra up to that time.

Pellagrin 1133: W. B., boy, was born in 1911. The initial attack occurred in the spring of 1912 at the approximate age of 1 year, according to the history. The disease recurred in 1913 and there was a severe recurrence again in the early spring of 1914, with good recovery. This patient was seen by us for the first time in September, 1914, at which time there were, of course, no recognizable signs of pellagra.

Pellagrin 1164: O. M. D., boy, was born Dec. 27, 1912. The pellagrous erythema appeared on the hands, forearms, feet and legs in June, 1914, at the age of 18 months, but it was preceded by a persistent gastro-intestinal disorder, manifested by vomiting and diarrhea, which began March 30. Evidence of very typical desquamation was still present when seen by us Sept. 30, 1914. There were no other recognized cases of pellagra in the household. The family lived on a farm and the nearest known pellagrin was an aunt of the baby, Pellagrin 29, living two miles away, who suffered her first attack in 1910, with recurrences each year. A history of association with this aunt was not obtainable.

Pellagrin 1220: A. R. P., girl, was born Sept. 5, 1913. The onset of pellagra occurred in August, 1914, at the age of 11 months, with erythema on backs of hands, which later extended up the arms to the shoulders. When seen on October 3, there was still some desquamation on the arms and shoulders and the condition was considered to be pellagra, although an absolutely positive diagnosis could not be made from the appearance at that time. The child was still nursing its mother, but had also been taking solid food, chiefly wheat bread and sweet potato, for several months. The child's father, Pellagrin 1134, had his first attack of pellagra in June, 1913, about three months before the birth of the child and he suffered a recurrent attack in the summer of 1914. The mother of this child and a brother, aged 4, have shown no signs of pellagra.

The data in regard to these fourteen cases are briefly summarized in Table 6.

Certain characteristics of pellagra in early life are illustrated by these cases. In the first place, there are here only two examples of pellagra as early as the seventh month. Neither of these two patients was seen by us until some years after the onset of pellagra and in one case, Pellagrin 645, we have no authority for the diagnosis at this early age except the statements of members of the family. The subsequent history makes it very certain that the patient actually suffered from pellagra, but does not make certain the time of onset. The other case, Pellagrin 888, seems to be better established as an actual instance of onset at age of 6 months. During our field investigations we made a special search for infantile cases of pellagra and neglected no opportunity to see them. Most of the infantile cases reported to us proved

disappointing upon closer examination. We feel very certain therefore that definitely recognizable cases of pellagra in children under the age of 12 months have been extremely rare in Spartanburg County.

Another feature of interest is the evidence of very intimate association or the presence of an antecedent case of pellagra in the household where the infant has contracted the disease. In three instances, Pellagrins 173, 645 and 941, the mother had been a pellagrin for several months before the child developed the disease; in one instance the mother came down with pellagra at about the same time as the child, Pellagrin 184. In this latter case the disease was evidently introduced into the household by a paternal aunt visiting there. In another

TABLE 6.—The Fourteen Pellagrins in Whom the Disease Appeared Before the Age of 2 Years

Pellagrin No.	Born	Onset of Pellagra	Age at Onset, Mos.	Recurrences	Authority for Diagnosis
645	Sept. 1909	Mar. 1910	6	1912, 1913	History only
888	Aug. 1908	Mar. 1909	6	1910, 1911, 1912, 1913, 1914	Dr. J. J. Allen
1,220	Sept. 1913	Aug. 1914	11	.....	Seen, Oct. 3, 1914
672	1910	1911	12(?)	None	History only
1,133	1911	Spring 1912	12(?)	1913, 1914	History only
173	Mar. 1910	June 1911	15	None	Dr. J. W. Babock
184	Mar. 1911	June 1912	15	Death, 1912	Dr. J. C. Moore
1,164	Dec. 1912	June 1914	18	.....	Seen
120	Oct. 1909	June 1911	19	Death, 1912	Dr. A. W. Nelson
179	June 1910	Feb. 1912	20	1913, 1914, D.	Seen
1,010	Oct. 1912	July 1914	20	.....	Seen
1,026	Nov. 1912	July 1914	20	.....	Seen
941	June 1912	May 1914	22	.....	Seen
643	Aug. 1907	July 1909	22	1910	History only

instance, Pellagrin 672, the paternal grandfather was the earlier case in the household; in two instances, Pellagrins 1,026 and 1,220, the child's father seems to have brought pellagra into the family. In one instance, Pellagrin 179, the earliest known case in the family was a sister, aged 4 years. Following this, the disease appeared in an aunt living in the same house, and after separation from this aunt the disease appeared in the young child, Pellagrin 179. In one instance, Pellagrin 120, the child developed pellagra simultaneously with an unrelated woman living in the same house, the nearest antecedent case being next door. In five instances, Pellagrins 643, 888, 1,010, 1,133 and 1,164 there were no other known pellagrins in the household. Three of these

cases (643, 888 and 1,133) arose previous to the beginning of our field work and their environments at the time could not be investigated. A fourth case, Pellagrin 1,010, originated in a neighboring county and the family moved into Spartanburg County on July 20, 1914, left the baby in the hospital and disappeared without giving us opportunity to obtain the desired information and about three weeks later the child was removed from the hospital by an aunt, who left no address. The fifth case, Pellagrin 1,164, originated in an isolated farm house, the nearest known pellagrin being an aunt two miles away, with whom there was no evident association. This series of cases in young children, therefore, furnishes more definite evidence of the dependence of incident pellagra upon close association with a preexisting case of the disease than is ordinarily found in the study of the disease as it originates in adults. This more clear-cut picture might be expected because of the relatively limited social intercourse of children under two years of age. It seems probable also that the incubation period of the disease is shorter and less variable in these young children than in older persons, which may also tend to simplify the problem.

It is interesting to note that in only four instances was the mother known to have pellagra and in only one instance, Pellagrin 645, did she have the disease previous to the birth of the child. When we bear in mind the relatively enormous prevalence of pellagra among child-bearing women in the endemic areas, it would seem remarkable that the simultaneous occurrence of pellagra in mother and infant child should be rare. A pellagrous father, grandfather, aunt or unrelated visitor in the household, considering the relative frequency of such association, seems to be as significant as the presence of a pellagrous mother. Child-bearing women make up a very large proportion of the cases of pellagra in Spartanburg County and an acute attack of pellagra is very frequently seen during the puerperium. The fact that young infants so rarely have pellagra and that only three children under the age of two years contracted the disease subsequent to its appearance in their mothers seems highly significant and indicates that the milk of pellagrous women cannot be regarded as an important agency in causing pellagra, either in the rôle of a vehicle of the hypothetical specific infectious or toxic causative agent or as a food deficient in elements, to the lack of which pellagra may be ascribed. Indeed one occasionally sees a happy, fat and healthy infant, whose only food has come from the breast of a pellagrous mother lying on her death-bed, and even if not well nourished and happy, it is nevertheless the rule for the children of pellagrous women to remain free from any sign of pellagra during infancy and especially during the period of exclusive breast-feeding. To those who are familiar with infantile beriberi and

its enormous prevalence and death rate in the Philippine Islands,[6] the contrast between infantile pellagra and infantile beriberi will be sufficiently striking.

Of the fourteen cases, only one died in the initial attack of pellagra and this one was the only negro child in the group. All white children survived the year of onset. One of them, Pellagrin 184, died the following April of acute dysentery, without recurrence of skin lesions. Another, Pellagrin 179, survived the initial attack and a recurrence the following year and died in the third summer after the disease had recurred. The remaining eleven children were alive at our last observation of them.

In the age period between 2 and 12 years there were 198 instances of onset of pellagra. Their distribution according to race, sex and age at onset is shown graphically in Figures 2, 3, 4 and 5 and the data are printed, along with the data for the fourteen younger children, in Table 7. It will be noted that 212 of the total 1,180 recorded cases, or nearly 18 per cent., had their onset before the age of 12 years. This is important when we recall how little attention has been paid, relatively, to pellagra in children living in their own homes. Of the 212 children, 204 were white and eight were colored, a ratio of 25.5 to 1, indicating that pellagra in this county has been relatively much more rare in negro children than in adult negroes. This is in accord with the hypothesis previously suggested, that pellagra has not as yet established itself as an endemic disease among the negroes of this county

6. The age distribution of deaths from beriberi in Manila, according to the government reports compiled from data in Quarterly Report of Bureau of Health of the Philippine Islands is as shown in the following tabulation:

Age	1912			1913			1914		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Under 1	397	490	887	317	370	687	389	510	899
1 to 4	29	27	56	7	13	20	20	8	28
5 to 9	2	2	4	7	4	11	2	4	6
10 to 14	5	3	8	1	3	4	1	1	2
15 to 19	3	16	19	3	8	11	5	11	16
20 to 29	7	11	18	10	6	16	13	6	19
30 to 39	10	16	26	12	13	25	14	17	31
40 to 49	4	26	30	5	27	32	3	17	20
Over 50	14	28	42	10	12	22	6	15	21
Total	471	619	1,090	372	456	828	453	589	1,042

to the same degree as in the white race. The negro children, being the most completely segregated portion of their race, are relativly least afflicted with pellagra.

In the whole group of 212 children there were seven deaths in the year of the initial attack: three in white girls, age at onset being 4, 8 and 10 years; two in white boys, age at onset being 3 and 11 years; two in colored boys, age at onset being 1 and 5 years, respectively. The indicated death rate in first attack for children under 12 years is therefore quite low, 2.5 per cent. for white children, 25 per cent. for colored children and 3.3 per cent. for all the children considered together. The group of pellagrins originating in the age period from 2 to 12 years is of peculiar interest because of the large number of cases and the low mortality in the year of onset.

TABLE 7.—Pellagrins with Onset at Age Below 12 Years, Distributed According to Race, Sex and Age at Onset of the Initial Erythema

	Age in Years												
	0	1	2	3	4	5	6	7	8	9	10	11	Total
White girls.....	1	4	7	12	17	6	11	11	9	10	7	4	99
White boys.....	2	6	12	8	14	8	19	9	5	8	8	5	104
Colored girls....	0	0	0	0	0	0	1	0	0	1	0	0	2
Colored boys...	0	1	0	0	1	1	0	1	0	2	0	0	6
Total.....	3	11	20*	20	32	15	31	21	14	21	15	0	212*

* Including one white child, aged 2, of unknown sex.

The age period from 12 to 16 years shows only twenty-one initial attacks of pellagra, nine in white girls, eleven in white boys and one in a colored girl aged 15. Of the twenty-one incident cases, only one died in the year of onset, Pellagrin 475, a white girl, aged 13. The low incidence of pellagra in these four years is in marked contrast to the incidence in younger persons of both sexes and to that in older women.

Up to the age of 16, the difference between boys and girls has been slight, although one may see indication of a greater tendency for boys to get pellagra under the age of 3. The greatest contrast on the other hand is shown between the white race and the colored race. Of the whole group of 233 incident cases under 16 years of age, 224 were white and only nine were colored persons, a ratio of 25 to 1. Taken in connection with the undoubtedly inferior food of the negroes in this county, as regards quality, quantity and variety, together with the

equally certain greater relative segregation of the negro children from association with pellagrins, these facts seem highly significant for the problem of the etiology of pellagra and may not be without value in considering the prevention of the disease. After the age of 16 the sex distinction in pellagra incidence becomes very prominent, but the racial relationships are not without interest. The distribution of the incident cases in the four years from age 16 to age 20 is shown in Table 8. The remarkable difference in sex incidence of pellagra in this population, namely the great excess of female pellagrins over male pellagrins, has been pointed out in our previous reports. Here it is strikingly shown that this difference becomes manifest at about the seventeenth year of life and the change from the relative equality of the earlier years is a sharp one.

TABLE 8.—PELLAGRINS WITH INITIAL ATTACK BETWEEN AGES 16 AND 20, DISTRIBUTED ACCORDING TO RACE, SEX AND AGE AT ONSET

	Age in Years				
	16	17	18	19	Total
White women	8	12	13	12	45
White men	9	3	2	1	6
Colored women	3	3	5	4	15
Colored men	0	1	1	0	2
Total women	10	16	18	16	60
Total men	0	4	3	1	8
Grand total	10	20	21	17	68

Another remarkable feature of the table is the relatively high incidence in colored women, fifteen colored women and forty-five white women, a ratio of 1 to 3. Previous to the age 16, in the data considered above, there were three colored girls, one of them 15 years old, and 108 white girls, the ratio being 1 to 36. The enormous rise in pellagra incidence in negro women in the age period from 16 to 20 years is not only very great as compared with younger negroes, but it is relatively enormous in comparison even with the large increase in incidence in white women which takes place at this time. Among the possible explanations for this greater increase in pellagra incidence in adolescent colored women, may be mentioned the somewhat earlier and somewhat more sudden change to the adult state in the negro race. This may play some part. Another possible factor, which seems to us of great importance, is the closer association with the white race which

the negro women experience at about this time. Many of them are engaged in domestic service or as day nurses to care for children. In many instances childbearing begins before the age of twenty, and this may also play a part. It has been impossible to get reliable histories in most of these cases of colored women, and it seems not worth while to go into details in regard to them. In only a few cases was there evidence of close association with antecedent cases of pellagra and in only three instances were there earlier cases of pellagra in the household. In three other instances a history of domestic service, such as cooking and washing clothes for mill-village people, was obtained. One patient gave birth to an illegitimate child in the year following the onset of pellagra.

The deaths during the year of initial attack for the age period 16 to 20 years are shown in Table 9. The characteristic racial difference in death rate is again evident here.

TABLE 9.—Death Rate from Pellagra During the Year of Initial Attack in the Age Period 16 to 20 Years

	White			Colored			Both Races		
	Women	Men	Total	Women	Men	Total	Women	Men	Total
Initial attacks...	45	6	51	15	2	17	60	8	68
Deaths in initial attack..	3	0	3	7	1	8	10	1	11
Mortality per cent.	6.7	0 0	5.9	46.7	50.0	47.1	16.7	12.5	16.2

From the age of 20 years to that of 50 years the women show a very much higher incidence of pellagra than the men, the disparity being greater in the earlier years and gradually approaching equality at age 50. The number of initial attacks in each five-year period after age 20 is shown in Table 10. The number of female pellagrins is enormously greater than the number of male pellagrins in the third decade of life, but in the later age periods the number of women attacked diminishes rapidly while the number of men increases somewhat, and after age 55 years the female pellagrins are actually less numerous than the male.

The death rate in year of initial attack for each race and sex, by decades after age 20, is shown in Table 11. For the women the figures are large enough to indicate a consistent increase in the death rate in initial attack correlated with increased age at onset, ranging from 4.6 per cent. in the third decade to 47.6 per cent. in the seventh decade. For the other three groups the number of cases is somewhat small and deductions correspondingly less reliable. The death rate

TABLE 10.—Initial Attacks of Pellagra in Each Race and Sex by Five-Year Periods After Age 20

Age	White			Colored			Both Races		
	Women	Men	Total	Women	Men	Total	Women	Men	Total
20 to 24	106	10	116	27	4	31	133	14	147
25 to 29	111	14	125	15	2	17	126	16	142
30 to 34	102	17	119	21	2	23	123	19	142
35 to 39	72	23	95	9	4	13	81	27	108
40 to 44	58	25	83	5	0	5	63	25	88
45 to 49	29	19	48	6	2	8	35	21	56
50 to 54	26	24	50	6	4	10	32	28	60
55 to 59	18	25	43	4	2	6	22	27	49
60 to 64	15	17	32	1	4	5	16	21	37
65 to 69	6	6	12	2	3	5	8	9	17
70 to 74	2	6	8	0	0	0	2	6	8
75 to 79	1	2	3	0	0	0	1	2	3
80 to 84	0	1	1	0	1	1	0	2	2
85 to 89	0	0	0	1	0	1	1	0	1

TABLE 11.—Deaths in Year of Onset of Pellagra for Each Race and Sex, According to Age by Decades After Age 20

	Decades							
	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 to 89	Total
White Women								
Initial attacks	217	174	87	44	21	3	0	546
Deaths	10	17	13	14	10	1	0	65
Rate, per cent.	4.6	9.8	14.9	31.8	47.6	32.3	.....	11.9
White Men								
Initial attacks	24	40	44	49	23	8	1	189
Deaths	4	8	7	12	5	3	1	40
Rate, per cent.	16.7	20.0	15.9	24.5	21.7	37.5	100.0	21.2
Colored Women								
Initial attacks	42	30	11	10	3	0	1	97
Deaths	13	13	7	4	2	0	0	39
Rate, per cent.	31.0	43.3	63.6	40.0	66.7	.....	0.0	40.2
Colored Men								
Initial attacks	6	6	2	6	7	0	1	28
Deaths	2	3	0	3	5	0	1	14
Rate, per cent.	33.3	50.0	0.0	50.0	71.4	.....	100.0	50.0

TABLE 12.—Distribution, According to Race, Sex and Age at Onset of Initial Erythema, of the 187 Pellagrins Who Died in the Year of the Initial Attack

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	1	1	0	1	1
2	0	0	0	0	0	0	0	0	0
3	0	1	1	0	0	0	0	1	1
4	1	0	1	0	0	0	1	0	1
5	0	0	0	0	1	1	0	1	1
6	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0
8	1	0	1	0	0	0	1	0	1
9	0	0	0	0	0	0	0	0	0
10	1	0	1	0	0	0	1	0	1
11	0	0	0	0	0	0	0	0	0
12	0	1	1	0	0	0	0	1	1
13	1	0	1	0	0	0	1	0	1
14	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0
16	1	0	1	2	0	2	3	0	3
17	0	0	0	1	0	1	1	0	1
18	1	0	1	3	1	4	4	1	5
19	1	0	1	1	0	1	2	0	2
20	0	0	0	0	0	0	0	0	0
21	3	1	4	0	0	0	3	1	4
22	0	1	1	1	1	2	1	2	3
23	0	0	0	4	0	4	4	0	4
24	2	1	3	3	0	3	5	1	6
25	2	1	3	4	0	4	6	1	7
26	0	0	0	1	0	1	1	0	1
27	1	0	1	0	0	0	1	0	1
28	0	0	0	0	1	1	0	1	1
29	2	0	2	0	0	0	2	0	2
30	1	0	1	4	1	5	5	1	6
31	1	0	1	0	0	0	1	0	1
32	1	1	2	1	0	1	2	1	3
33	3	0	3	1	0	1	4	0	4
34	3	2	5	1	0	1	4	2	6
35	2	2	4	1	1	2	3	3	6
36	2	1	3	4	0	4	6	1	7
37	2	1	3	0	0	0	2	1	3
38	1	0	1	0	1	1	1	1	2
39	1	1	2	1	0	1	2	1	3
40	5	3	8	2	0	2	7	3	10
41	1	0	1	0	0	0	1	0	1
42	2	1	3	0	0	0	2	1	3
43	1	0	1	0	0	0	1	0	1
44	0	0	0	1	0	1	1	0	1
45	0	2	2	1	0	1	1	2	3
46	3	1	4	2	0	2	5	1	6
47	1	0	1	0	0	0	1	0	1
48	0	0	0	0	0	0	0	0	0
49	0	0	0	1	0	1	1	0	1
50	2	3	5	2	2	4	4	5	9
51	0	0	0	0	0	0	0	0	0
52	2	3	5	0	1	1	2	4	6
53	1	1	2	1	0	1	2	1	3
54	1	2	3	0	0	0	1	2	3
55	2	1	3	1	0	1	3	1	4
56	2	1	3	0	0	0	2	1	3
57	0	1	1	0	0	0	0	1	1
58	3	0	3	0	0	0	3	0	3
59	1	0	1	0	0	0	1	0	1

TABLE 12.—Distribution, According to Race, Sex and Age at Onset of Initial Erythema, of the 187 Pellagrins Who Died in the Year of the Initial Attack—(*Continued*)

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
60	3	0	3	0	3	3	3	3	6
61	2	0	2	0	0	0	2	0	2
62	0	1	1	0	0	0	0	1	1
63	2	1	3	0	0	0	2	1	3
64	0	2	2	0	0	0	0	2	2
65	2	0	2	0	0	0	2	0	2
66	1	0	1	0	0	0	1	0	1
67	0	1	1	0	1	1	0	2	2
68	0	0	0	2	1	3	2	1	3
69	0	0	0	0	0	0	0	0	0
70	1	2	3	0	0	0	1	2	3
71	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0
75	0	1	1	0	0	0	0	1	1
76	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0
80	0	0	0	0	1	1	0	1	1
81	0	0	0	0	0	0	0	0	0
82	0	1	1	0	0	0	0	1	1
83	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0
Total, age known.	72	42	114	46	17	63	118	59	177
Age unknown	6	3	9	1	0	1	7	3	10
Total	78	45	123	47	17	64	125	62	187

in first attack seems to be more uniform for the white men, but there is some increase toward old age and the death rate of the whole group is nearly twice as high as for the white women. In the negroes over 20 years of age the death rate in first attack is nearly 50 per cent., somewhat higher for men than women and somewhat higher in the later decades of life. The number of cases available here is small, especially in the group of colored men.

In Table 12 are presented the detailed data in regard to race, sex and age at onset of pellagra of all the 187 patients who died in the year of the initial attack.

AGE DISTRIBUTION OF PELLAGRINS INCIDENT IN EACH YEAR

The distribution according to race, sex and age at onset, by five-year periods, of the incident cases of pellagra in each year after 1907 and for all those with onset previous to 1908, is shown in detail in Table 13. The data of these tables, although summarized into five-year

TABLE 13.—The Distribution of Initial Attacks of Pellagra in Different Years, According to Race, Sex and Age at Time of Onset, by Five-Year Age Periods

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Before 1908									
0 to 4	1	0	1	0	0	0	1	0	1
5 to 9	0	0	0	0	0	0	0	0	0
10 to 14	0	0	0	0	0	0	0	0	0
15 to 19	3	0	3	2	0	2	5	0	5
20 to 24	10	0	10	0	0	0	10	0	10
25 to 29	2	0	2	0	0	0	2	0	2
30 to 34	5	1	6	1	1	2	6	2	8
35 to 39	5	1	6	1	0	1	6	1	7
40 to 44	4	3	7	0	0	0	4	3	7
45 to 49	4	1	5	0	0	0	4	1	5
50 to 54	3	1	4	1	0	1	4	1	5
55 to 59	2	3	5	0	0	0	2	3	5
60 to 64	0	2	2	0	0	0	0	2	2
65 to 69	0	0	0	0	0	0	0	0	0
Over 70	0	0	0	0	0	0	0	0	0
Age unknown	0	0	0	0	0	0	0	0	0
Total.....	39	12	51	5	1	6	44	13	57
1908									
0 to 4	0	0	0	0	0	0	0	0	0
5 to 9	1	1	2	0	0	0	1	1	2
10 to 14	0	0	0	0	0	0	0	0	0
15 to 19	1	0	1	0	0	0	1	0	1
20 to 24	6	0	6	0	0	0	6	0	6
25 to 29	5	0	5	0	0	0	5	0	5
30 to 34	3	0	3	0	0	0	3	0	3
35 to 39	0	0	0	0	0	0	0	0	0
40 to 44	0	1	1	0	0	0	0	1	1
45 to 49	1	0	1	0	0	0	1	0	1
50 to 54	0	0	0	0	0	0	0	0	0
55 to 59	0	0	0	0	0	0	0	0	0
60 to 64	0	0	0	0	0	0	0	0	0
65 to 69	0	0	0	0	0	0	0	0	0
Age unknown	1	0	1	0	0	0	1	0	1
Total.....	18	2	20	0	0	0	18	2	20

TABLE 13.—The Distribution of Initial Attacks of Pellagra in Different Years, According to Race, Sex and Age at Time of Onset, by Five-Year Age Periods—(*Continued*)

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
1909									
0 to 4	1	1	2	0	0	0	1	1	2
5 to 9	0	0	0	0	0	0	0	0	0
10 to 14	0	0	0	0	0	0	0	0	0
15 to 19	1	0	1	2	0	2	3	0	3
20 to 24	9	0	9	0	0	0	9	0	9
25 to 29	7	0	7	0	0	0	7	0	7
30 to 34	5	0	5	0	0	0	5	0	5
35 to 39	5	1	6	0	0	0	5	1	6
40 to 44	1	2	3	0	0	0	1	2	3
45 to 49	1	2	3	0	0	0	1	2	3
50 to 54	3	4	7	1	0	1	4	4	8
55 to 59	3	2	5	0	0	0	3	2	5
60 to 64	1	1	2	0	0	0	1	1	2
65 to 69	0	2	2	0	1	1	0	3	3
Over 70	0	0	0	0	0	0	0	0	0
Age unknown	0	1	1	0	0	0	0	1	1
Total.....	37	16	53	3	1	4	40	17	57
1910									
0 to 4	2	2	4	0	0	0	2	2	4
5 to 9	3	3	6	1	1	2	4	4	8
10 to 14	0	1	1	0	0	0	0	1	1
15 to 19	11	1	12	2	0	2	13	1	14
20 to 24	9	1	10	5	2	7	14	3	17
25 to 29	19	1	20	2	1	3	21	2	23
30 to 34	14	2	16	1	0	1	15	2	17
35 to 39	5	3	8	1	0	1	6	3	9
40 to 44	8	1	9	0	0	0	8	1	9
45 to 49	4	1	5	1	0	1	5	1	6
50 to 54	6	4	10	0	0	0	6	4	10
55 to 59	3	3	6	1	0	1	4	3	7
60 to 64	3	4	7	0	0	0	3	4	7
65 to 69	2	0	2	1	0	1	3	0	3
Over 70	1	2	3	0	0	0	1	2	3
Age unknown	3	1	4	0	0	0	3	1	4
Total...	93	30	123	15	3	18	108	33	141

TABLE 13.—The Distribution of Initial Attacks of Pellagra in Different Years, According to Race, Sex and Age at Time of Onset, by Five-Year Age Periods—(*Continued*)

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
1911									
0 to 4	5	12	18*	0	0	0	5	12	18*
5 to 9	5	5	10	0	1	1	5	6	11
10 to 14	2	8	10	0	0	0	2	8	10
15 to 19	11	3	14	1	1	2	12	4	16
20 to 24	20	1	21	3	0	3	23	1	24
25 to 29	24	3	27	5	0	5	29	3	32
30 to 34	21	2	23	4	1	5	25	3	28
35 to 39	16	6	22	1	0	1	17	6	23
40 to 44	17	6	23	0	0	0	17	6	23
45 to 49	6	5	11	0	1	1	6	6	12
50 to 54	3	4	7	2	0	2	5	4	9
55 to 59	3	8	11	2	0	2	5	8	13
60 to 64	2	2	4	0	1	1	2	3	5
65 to 69	2	0	2	0	0	0	2	0	2
Over 70	0	3	3	0	1	1	0	4	4
Age unknown	3	0	3	1	0	1	4	0	4
Total.....	140	68	209*	19	6	25	159	74	234*
1912									
0 to 4	9	7	16	0	1	1	9	8	17
5 to 9	11	14	25	1	0	1	12	14	26
10 to 14	7	3	10	0	0	0	7	3	10
15 to 19	10	1	11	3	0	3	13	1	14
20 to 24	11	3	14	8	1	9	19	4	23
25 to 29	14	4	18	1	0	1	15	4	19
30 to 34	15	6	21	6	0	6	21	6	27
35 to 39	17	2	19	0	0	0	17	2	19
40 to 44	9	8	17	1	0	1	10	8	18
45 to 49	2	5	7	1	0	1	3	5	8
50 to 54	2	1	3	0	2	2	2	3	5
55 to 59	2	7	9	1	0	1	3	7	10
60 to 64	4	3	7	1	0	1	5	3	8
65 to 69	0	1	1	0	1	1	0	2	2
Over 70	0	1	1	1	0	1	1	1	2
Age unknown	3	0	3	0	0	0	3	0	3
Total.....	116	66	182	24	5	29	140	71	211

* Including one white child aged 2, sex unknown.

TABLE 13.—The Distribution of Initial Attacks of Pellagra in Different Years, According to Race, Sex and Age at Time of Onset, by Five-Year Age Periods—(*Continued*)

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
1913									
0 to 4	13	10	23	0	0	0	13	10	23
5 to 9	9	11	20	0	1	1	9	12	21
10 to 14	4	6	10	0	0	0	4	6	10
15 to 19	6	2	8	2	1	3	8	3	11
20 to 24	24	4	28	4	1	5	28	5	33
25 to 29	27	4	31	4	2	6	31	6	37
30 to 34	27	1	28	6	0	6	33	1	34
35 to 39	15	5	20	4	2	6	19	7	26
40 to 44	9	2	11	2	0	2	11	2	13
45 to 49	5	4	9	1	1	2	6	5	11
50 to 54	6	5	11	1	1	2	7	6	13
55 to 59	3	0	3	0	1	1	3	1	4
60 to 64	4	2	6	0	3	3	4	5	9
65 to 69	0	2	2	0	0	0	0	2	2
Over 70	1	0	1	0	0	0	1	0	1
Age unknown	1	1	2	1	0	1	2	1	3
Total.....	154	59	213	25	13	38	179	72	251
1914									
0 to 4	10	10	20	0	1	1	10	11	21
5 to 9	18	15	33	0	1	1	18	16	34
10 to 14	5	4	9	0	0	0	5	4	9
15 to 19	4	1	5	4	0	4	8	1	9
20 to 24	17	1	18	7	0	7	24	1	25
25 to 29	13	2	15	3	0	3	16	2	18
30 to 34	12	5	17	3	0	3	15	5	20
35 to 39	9	5	14	2	2	4	11	7	18
40 to 44	10	2	12	2	0	2	12	2	14
45 to 49	6	1	7	3	0	3	9	1	10
50 to 54	3	5	8	1	1	2	4	6	10
55 to 59	2	2	4	0	1	1	2	3	5
60 to 64	1	3	4	0	0	0	1	3	4
65 to 69	2	1	3	1	1	2	3	2	5
Over 70	1	3	4	0	0	0	1	3	4
Age unknown	2	1	3	0	0	0	2	1	3
Total	115	61	176	26	7	33	141	68	209

periods, are still too detailed to give an immediate impression of the differences. The marked increase in pellagra up to 1911 and the somewhat slower increase since that time have been commented upon. Attention has also been called to the indication that relatively more negroes have been attacked in recent years. We wish, in this place, to direct especial attention to the age distribution.

TABLE 14.—Summary of Age Distribution of Initial Attacks in Different Years

	Age						Total
	0 to 9	10 to 14	15 to 19	20 to 49	Over 50	Unknown	
Before 1908	1	0	5	39	12	0	57
1908	2	0	1	16	0	1	20
1909	2	0	3	33	18	1	57
1910	12	1	14	80	30	4	141
1911	29	10	16	142	33	4	234
1912	43	10	14	114	27	3	211
1913	44	10	11	154	29	3	251
1914	55	9	9	105	28	3	209
Total	188	40	73	683	177	19	1,180

TABLE 15.—Proportion of Initial Attacks in Children Under 12 Years of Age

	Before 1910	1910	1911	1912	1913	1914	Total
Total incident pellagrins	134	141	234	211	251	209	1,180
Incident pellagrins under 12 years	5	13	33	48	51	62	212
Per cent.	3.7	9.2	14.1	22.7	20.3	29.7	18.0

The striking differences in age distribution of initial attacks of pellagra are shown in Table 14. In the early years, up to 1910, there were in the series only five cases in children out of a total of 134 cases, or 3.7 per cent. The ratio between initial attacks in children under 12 years and total initial attacks for each year after 1909 is shown in Table 15. It is evident that the proportion of children attacked by pellagra has increased very much since 1909 and that the proportion was greatest in 1914, when nearly 30 per cent. of the new cases were in children. This increase is in part only apparent because of the lack of attention to pellagra in children during the years previous to 1912,

but in a considerable degree, we believe, it represents a real increase in the proportion of children attacked by the disease. The actual number of children attacked shows a progressive increase each year to 1914, in which year sixty-two children are known to have contracted the disease.

It is well recognized that endemic areas of pellagra in noninstitutional populations are characterized by the presence of pellagrous children. This point has been emphasized by Sambon.[7] Our observations of pellagra have also convinced us that the sporadic cases of pellagra and the first cases in a community are almost certain to occur in adults. The appearance of the disease in children, unless they are recent arrivals, at once suggests that the disease has gained a local foothold and that undoubted new cases are actually originating in the locality. In adults the actual place and time of origin is much less certain. We have in our series of cases several pellagrins in whom a recurrence appeared after two or more years of freedom from diagnostic symptoms and there is one instance of definite severe attack of pellagra in a woman, aged 61, in the year 1913, who gives a very clear history of similar attacks in the summers of 1893, 1894 and 1895, with complete absence of symptoms for eighteen years. Incidentally, it may be mentioned that this old woman recovered from the 1913 attack and has remained free from the eruption in 1914 and 1915. The occurrence of such cases as this calls into question to some extent the decision concerning place of origin of the disease in adults who have changed their place of abode. In children, on the other hand, the length of previous life is shorter and in most instances the individuals have remained within a relatively small area throughout life. We are inclined, also, to believe that the incubation period of pellagra is shorter and more uniform in children.

The rapid and progressive increase of pellagra in children in Spartanburg County may therefore be regarded as additional evidence of the rather recent extension of the disease in this area and as an indication that pellagra has been and is even now becoming more firmly established as an endemic disease of this locality. In other words, more homes and more families are now afflicted with this disease than in previous years.

INCIDENCE OF PELLAGRA PER 10,000 POPULATION

The population of Spartanburg County, according to the U. S. Census,[8] was 65,560 in 1900 and 83,465 in 1910. If this increase continued at the same arithmetical rate after 1910, there has been added

7. Sambon, L. W.: Progress Report on the Investigation of Pellagra, Jour. Trop. Med., 1910, xiii, 271, 287, 305, 319.

8. Thirteenth Census of the United States, 1910, iii, 664.

to this population 7,162 individuals from 1910 to 1914, and the estimated population in 1914 would be therefore 90,626. The same census shows that the colored population of the county was 21,167 in 1900 and 26,410 in 1910. The colored population in 1914, estimated in the same way, would be 28,507. We have been able to obtain directly from the Census Bureau, through courtesy of the U. S. Department of Commerce, more detailed statistics of the exact distribution, according to race, sex and age, of the population under 20 years of age, as well as for the age periods 20 to 44 years, and over 45 years. These data were printed in our first progress report.[9] The U. S. Census[10] for 1910 also shows the composition of the population of the whole state according to race, sex and age by five-year age periods to age 65, and beyond that by decades. Assuming that the age distribution in the whole state was not significantly different from the age distribution in Spartanburg County, we have divided the known county groups from age 20 to 44 and the known county groups of age 45 and over into five-year and ten-year age periods in the same proportion. Then by applying the formula for the arithmetic increase to each group of the total population, male and female, and to each group of the colored population, male and female, we have calculated their distribution by age periods in 1914. The distribution of the white population, that is, all not colored, has then been obtained by difference. The resulting data doubtless indicate the number of individuals of each race for each age period in the county in 1914 as accurately as is possible in the absence of an actual census taken in that year. Certainly they are sufficiently accurate for our present purpose of estimating the relative incidence of pellagra in various age periods in relation to age and sex. These data are shown in Table 16.

The ratio of total recorded incident attacks of pellagra up to the end of 1914, for each race and sex in each age period, to the respective population of the county in 1914 is shown in Table 17, expressed as incident cases per 10,000 of population. The figures represent total recorded cases in the county and not incidence per year, the total number of cases considered here (1,180) being more than four times the number recorded as originating in any one year (251 in 1913). The data of these tables are presented graphically in Figure 6. These pictures are different from those shown in Figures 2, 3, 4 and 5, because here the number of pellagrins at each age period has been divided by the total population of that age period, and of course the total population is largest in the earliest age period and tends to dimin-

9. Siler, J. F., and Garrison, P. E.: An Intensive Study of the Epidemiology of Pellagra: Report of Progress, Am. Jour. Med. Sc., 1913, cxlvi, 44; First Progress Report, 1913, p. 19.

10. Thirteenth Census of the United States, 1910, iii, 654.

ish progressively to old age. Thus one finds that the twenty-five cases in white men in the age period 55 to 59 represent an incidence of 325 per 10,000 population at this age, whereas the forty-nine cases in the age period 5 to 9 represent an incidence of only 119 per 10,000 population at this age. The incidence rates for the white race for ages beyond

TABLE 16.—Population of Spartanburg County in 1914 by Five-Year Age Periods to Age 65 and Subsequently by Decades, Calculated from Data of U. S. Census of 1910 and 1900

Age	White, Including All not Colored			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0 to 4	4,641	4,935	9,576	2,126	2,222	4,348	6,767	7,157	13,924
5 to 9	4,008	4,116	8,124	2,030	2,031	4,061	6,038	6,147	12,185
10 to 14	3,592	3,789	7,381	1,980	1,933	3,913	5,572	5,722	11,294
15 to 19	3,576	3,501	7,077	1,685	1,649	3,334	5,261	5,150	10,411
0 to 19	**15,817**	**16,341**	**32,158**	**7,821**	**7,835**	**15,656**	**23,638**	**24,176**	**47,814**
20 to 24	3,132	2,943	6,075	1,689	1,359	3,048	4,821	4,302	9,123
25 to 29	2,485	2,381	4,867	1,232	1,028	2,260	3,718	3,409	7,127
30 to 34	1,906	1,972	3,878	871	780	1,651	2,777	2,752	5,529
35 to 39	1,687	1,782	3,469	809	758	1,567	2,496	2,540	5,036
40 to 44	1,237	1,328	2,565	580	561	1,141	1,817	1,889	3,706
20 to 44	**10,448**	**10,406**	**20,854**	**5,181**	**4,486**	**9,667**	**15,629**	**14,892**	**30,521**
45 to 49	1,092	1,003	2,095	412	350	762	1,504	1,353	2,857
50 to 54	1,009	1,091	2,100	331	367	698	1,340	1,458	2,798
55 to 59	702	769	1,471	213	233	446	915	1,002	1,917
60 to 64	663	756	1,419	209	301	510	872	1,057	1,929
65 to 74	736	678	1,414	221	280	501	957	958	1,915
75 to 84	250	184	434	71	73	144	321	257	578
85 to 94	42	28	70	18	16	34	60	44	104
95 and over	7	4	11	6	4	10	13	8	21
45 and over	**4,501**	**4,513**	**9,014**	**1,481**	**1,624**	**3,105**	**5,982**	**6,137**	**12,119**
Age unknown	42	51	93	37	42	79	79	93	172
Total.....	**30,808**	**31,311**	**62,119**	**14,520**	**13,987**	**28,507**	**45,328**	**45,298**	**90,626**

TABLE 17.—Relative Incidence of Pellagra in Respect to Race, Sex and Age at Onset, Based on Total Recorded Pellagrins up to Oct. 15, 1914, and Population of the County in 1914 Estimated by Computation from U. S. Census of 1900 and 1910

Age	White Race								
	Female			Male			Total		
	Population, 1914	Recorded Pellagrins	Incidence per 10,000	Population, 1914	Recorded Pellagrins	Incidence per 10,000	Population, 1914	Recorded Pellagrins	Incidence per 10,000
0 to 4	4,641	41	88	4,935	42	85	9,576	84*	88
5 to 9	4,008	47	117	4,116	49	119	8,124	96	118
10 to 14	3,592	18	50	3,789	22	58	7,381	40	54
15 to 19	3,576	47	131	3,501	8	23	7,077	55	78
0 to 19	**15,817**	**153**	**97**	**16,341**	**121**	**74**	**32,158**	**275***	**86**
20 to 24	3,132	106	338	2,943	10	34	6,075	116	191
25 to 29	2,486	111	447	2,381	14	59	4,867	125	257
30 to 34	1,906	102	535	1,972	17	86	3,878	119	307
35 to 40	1,687	72	427	1,782	23	129	3,469	95	274
40 to 44	1,237	58	469	1,328	25	188	2,565	83	324
20 to 44	**10,448**	**449**	**430**	**10,406**	**89**	**86**	**20,854**	**538**	**258**
45 to 49	1,092	29	266	1,003	19	189	2,095	48	229
50 to 54	1,009	26	258	1,091	24	220	2,100	50	238
55 to 59	702	18	256	769	25	325	1,471	43	292
60 to 64	663	15	226	756	17	225	1,419	32	226
65 to 74	736	6	82	678	12	177	1,414	18	127
75 to 84	250	2	80	184	3	163	434	5	115
85 to 94	42	1	238	28	0	0	70	1	143
Over 95	7	0	0	4	0	0	11	0	0
45 and over	**4,501**	**97**	**216**	**4,513**	**100**	**222**	**9,014**	**197**	**219**
Age unknown	42	13	.....	51	4	.....	93	17	.....
Total.....	**30,808**	**712**	**231**	**31,311**	**314**	**103**	**62,119**	**1,027***	**165**

* Including one child, aged 2, whose sex was not ascertained.

TABLE 17.—Relative Incidence of Pellagra in Respect to Race, Sex and Age at Onset, Based on Total Recorded Pellagrins up to Oct. 15, 1914, and Population of the County in 1914 Estimated by Computation from U. S. Census of 1900 and 1910—(*Continued*)

Colored Race

Age	Female			Male			Total		
	Population, 1914	Recorded Pellagrins	Incidence per 10,000	Population, 1914	Recorded Pellagrins	Incidence per 10,000	Population, 1914	Recorded Pellagrins	Incidence per 10,000
0 to 4	2,126	0	0	2,222	2	9	4,348	2	5
5 to 9	2,030	2	10	2,031	4	20	4,061	6	15
10 to 14	1,980	0	0	1,933	0	0	3,913	0	0
15 to 19	1,685	16	95	1,649	2	12	3,334	18	54
0 to 19	**7,821**	**18**	**23**	**7,835**	**8**	**10**	**15,656**	**26**	**17**
20 to 24	1,689	27	160	1,359	4	30	3,048	31	102
25 to 29	1,232	15	122	1,028	2	20	2,260	17	75
30 to 34	871	21	241	780	2	26	1,651	23	139
35 to 39	809	9	111	758	4	53	1,567	13	83
40 to 44	580	5	86	561	0	0	1,141	5	44
20 to 44	**5,181**	**77**	**149**	**4,486**	**12**	**27**	**9,667**	**89**	**92**
45 to 49	412	6	146	350	2	57	762	8	105
50 to 54	331	6	181	367	4	106	698	10	143
55 to 59	213	4	188	233	2	86	446	6	135
60 to 64	209	1	48	301	4	133	510	5	98
65 to 74	221	2	91	280	3	107	501	5	100
75 to 84	71	0	0	73	1	137	144	1	69
85 to 94	18	1	55	16	0	0	34	1	294
Over 95	6	0	0	4	0	0	10	0	0
45 and over	**1,481**	**20**	**135**	**1,624**	**16**	**100**	**3,105**	**36**	**116**
Age unknown	37	2	.....	42	0	.....	79	2	.....
Total.....	**14,520**	**117**	**81**	**13,987**	**36**	**25**	**28,507**	**153**	**54**

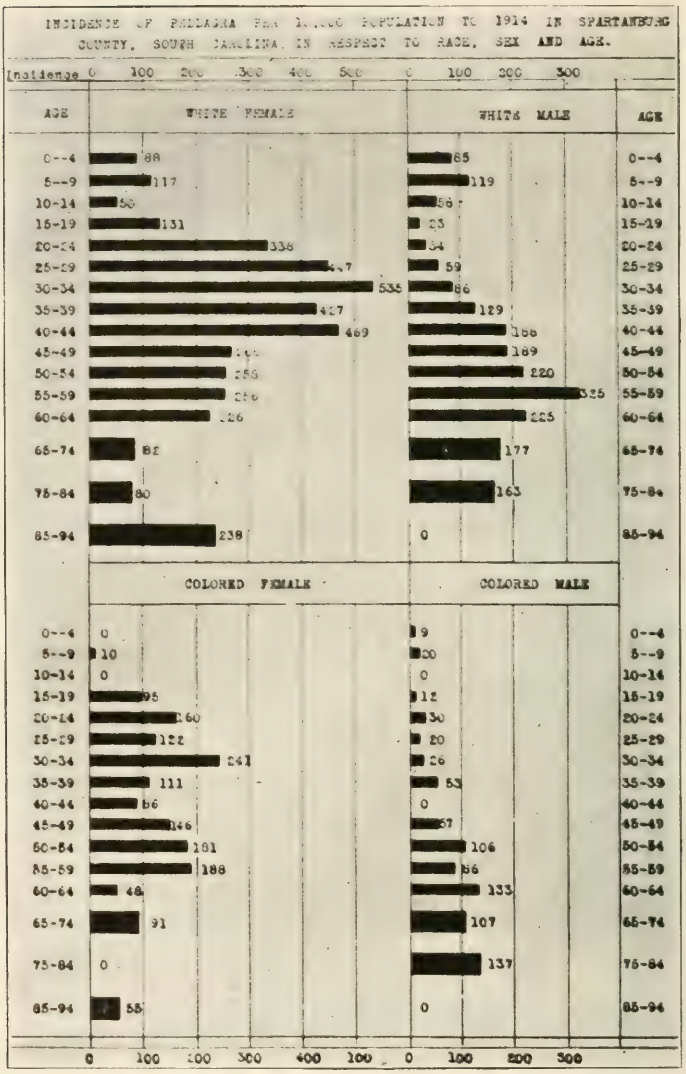

Fig. 6.—The incidence per 10,000 population has been computed from the calculated population of Spartanburg County in 1914 and the total recorded cases of pellagra in each five-year age period according to age at onset of the initial erythema. The broader columns after age of 65 apply to ten-year-age groups. The incidence per 10,000 for each age group is also indicated by the number placed at the end of the column.

age 75 and for the negro race beyond age 45 have little or no significance because of the very small groups of population.

In every instance there is a peak in the age period 5 to 9 followed by a fall in the period 10 to 14. In the next period, 15 to 19 years, the rise is sharp in the white female population, but especially sharp in the colored male and female. In fact it is in the ten years from 15 to 24 that the incidence of pellagra in negroes, both men and women, approaches most nearly the incidence rate of the disease in the white race of this county. In white women the rate ascends rapidly to reach the enormous incidence of 535 per 10,000 population in the age period 30 to 34, after which it gradually declines. The rate in white men ascends much more gradually, but in a progressive manner, reaching an incidence of 325 per 10,000 in the age period 55 to 59 years. In the negroes the incidence rate is everywhere lower than in the white race. For the negro women there is a rapid increase beginning at age 15 and reaching its height in the period 30 to 34 years, this being followed by a rapid decline and an irregular incidence beyond age 45, where the number of individuals is small. In negro men the number of individuals is so small that comparisons of different age periods are hardly warranted. The incidence rate on the whole is lower than that for any other of the three race-sex groups. Only after age 60 is there a distinct indication of a higher incidence in negro men than in negro women.

In this connection it may be mentioned that, next to negro children of both sexes, the adult negro men are most effectively segregated from social relationships with the white race in Spartanburg County, especially that portion of the white race which lives in the chief endemic foci of pellagra, namely, the cotton-mill villages. The adult negro man is to a very large extent a day laborer or a field worker in the open air, and his home is in general a cabin or a poorly constructed house, isolated on a farm or segregated in the negro quarter of a village or city. To this rule there are some exceptions, but they are relatively not numerous. The negro women also work in the field in many instances in addition to performing their household duties. Most of them are at some time employed by white families for domestic duties, some as house servants, but more in the capacity of washerwomen. The homes of the negro women are the same as the homes of the negro men and even when engaged as cooks and waitresses it is customary for the negro women to return to their homes at night. The data concerning food will, of course, be considered in a separate paper. It will suffice here to point out that the diet of the negroes is much inferior in quality, quantity and variety to that of the white race in this county.

In our opinion the relatively lower pellagra incidence in negroes in this county is due chiefly to their relative segregation from pel-

lagrins. They live in poorer houses, eat an inferior diet and are, as a whole, in much worse financial condition than the white race. On the other hand, they are socially segregated, their homes are for the most part either isolated cabins or are grouped in negro quarters of the city, town or village. Pellagra is not so persistently present among them as among the white race, furthermore, because the negro pellagrins die much more promptly than do the white pellagrins. The facts observed here in Spartanburg County in regard to racial and age differences in pellagra incidence indicate very strongly that poverty and poor diet are, as has long been known, factors of great moment in determining death rate from pellagra in those attacked, but that, as far as the original onset of the disease is concerned, they are of importance only in conjunction with close association with antecedent pellagrins or residence in an endemic area of the disease.

SUMMARY

1. The number of recognized incident cases of pellagra in Spartanburg County has increased progressively each year since 1907, very rapidly to 1911 and at a less rapid rate to 1914.

2. The death rate in year of initial attack was 15.8 per cent. for the total 1,180 recorded cases. There is no definite indication of a progressive change in the death rate in recent years, although it was apparently higher previous to 1911.

3. The disease has attacked the white race more than the negroes in this county, but in recent years there has been a slow but progressive increase in the ratio of incident negro pellagrins to incident white pellagrins.

4. The death rate in initial attack has been 41.8 per cent. for negroes and 12 per cent. for the white race.

5. Pellagra was very rarely observed under the age of 1 year. It was not so rare in the second year and fairly common in the age period from 2 to 12 years. The death rate in initial attack has been low in children.

6. Evidence of residence very close to an antecedent pellagrin has usually been quite clear in the cases of infantile pellagra.

7. The milk of pellagrous mothers cannot be regarded as the cause or the vehicle of the cause of pellagra in infants.

8. The age period 12 to 16 years is relatively free from initial attacks of pellagra.

9. After age 16 years pellagra incidence rises rapidly in women and the rise is especially sharp in colored women. In the latter group the death rate has been high, 46.7 per cent., in year of onset in the age period 16 to 20 years.

10. From age 20 to age 50 years, the number of women attacked by pellagra gradually diminishes and the number of men attacked gradually increases, so that the two sexes are approximately equal in this respect at age 50. In old age the onset of pellagra has been slightly more common in men in this population.

11. The death rate in first attack in white women over 20 years of age has been 11.9 per cent., increasing progressively from 4.6 per cent. in the third decade to 47.6 per cent. in the seventh decade of life. The death rate for analogous groups of white men, colored women and colored men has been 21.2 per cent., 40.2 per cent. and 50 per cent., respectively, with a slight tendency for the death rate to increase with age in all groups.

12. Pellagrins with onset under the age of 12 years were only 3.7 per cent. of the total recorded cases previous to 1910, but the proportion has increased to 29.7 per cent. of the total recorded onsets in the year 1914. These observations corroborate the other evidence of a distinct progressive increase of pellagra in this county in recent years.

13. The incidence per 10,000 population has been 231 for white female population, 103 for white male, 81 for colored female and 25 for colored male. In the age period 10 to 14 years the incidence is low in all groups. In white female population it is highest in the age period 30 to 34 years, namely 535 per 10,000; in white male, in the age period 55 to 59, namely 325 per 10,000; in colored female 241 per 10,000 in age period 30 to 34; in colored male 133 per 10,000 in age period 60 to 64.

14. The lower incidence rate and the higher death rate for those attacked have occurred in negroes in conjunction with greater poverty of this race and a diet poorer in quality, quantity and variety. Incidence has been lowest in the sex and age groups of negroes most completely segregated from white pellagrins.

THE LIME DEFICIENCY OF DIABETES*

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INTRODUCTION

Bocker[1] in 1853 and Neubauer[2] in 1856 reported that diabetic patients excreted more lime salts in their urine than normal individuals. In 1889 Toralbo[3] came to a similar conclusion from his findings. Since that time many observations have been recorded, and the conclusion has been reached that diabetics suffer from a loss of calcium from their body. Some of these studies we shall review in detail.

Von Moraczewski[4] in 1897 found in one case of diabetes mellitus, on a mixed diet, a retention of nitrogen and chlorin coincident with a loss of calcium and phosphorus, the phosphorus loss being nearly three times as great as the calcium loss. The phosphorus loss was 32 per cent. of the intake and the calcium loss 11 per cent. of the intake. On an animal diet containing much less chlorin and lime, and somewhat less phosphorus, the nitrogen balance remained positive, but the chlorin became negative, and the losses of phosphorus and calcium were increased. Von Moraczewski thought that the lime excretion was a specific symptom and that increasing the lime in the food decreased the sugar excretion.

A year later von Moraczewski[5] (1898) published further balance data on diabetes mellitus. When added to a mixed diet, calcium phosphate, 10 gm. per day, seemed to cause a retention of calcium, perhaps a slight increase in nitrogen storage, a reduced loss of phosphorus, and a reduced excretion of sugar, while sodium chlorid, 10 gm. per day, appeared to have an unfavorable influence on nitrogen, phosphorus and calcium balances. In a later paper (1903-4) von Moraczewski published urine analyses from three cases of diabetes mellitus on various diets. The ingestion of tricalcic phosphate was said again to have reduced the sugar excretion.

Erben[6] in 1907 found a decreased lecithin content of the blood in diabetes mellitus, and large amounts of alkalies and calcium. In a later

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1. Bocker: Deutsch. Klin., 1853, v, 359.
2. Neubauer: Jour. f. prakt. Chem., 1856, lxvii, 64, 83.
3. Toralbo: Riv. clin. e terap., 1889.
4. Von Moraczewski: Zentralbl. f. inn. Med., 1897, xviii, 921.
5. Von Moraczewski: Ztschr. f. klin. Med., 1898, xxxiv, 59.
6. Erben: Zentralbl. f. inn. Med., 1907, xxviii, 1090.

study he found the blood plasma with a normal lecithin content, but the erythrocytes with lecithin content reduced.

Towles[7] in 1910 found a lime deficiency in diabetes. Von Noorden[8] found an excretion of calcium, magnesium and phosphorus much in excess of the quantity in the food, and of phosphorus much in excess of that which would accompany the excreted nitrogen in the soft tissues; and concluded that this was due to catabolism of bone. A. R. Mandel and Lusk[9] in 1904 also found phosphorus elimination excessive in diabetes. Von Noorden cites the work of van Ackeren, showing that the bones atrophy as a whole, though von Noorden is of the opinion that these phenomena are not due simply to the action of an acid. Von Noorden also has shown an increased excretion of purin bodies in such severe diabetes as results in much destruction of tissues. He cites the work of Gaethgens[10] and Kulz,[11] showing that the natural parallelism between nitrogen and phosphorus of food and excreta usually exists, except where there is acidosis. Under this latter condition the phosphorus excretion, as previously noted, becomes supernormal in comparison with the nitrogen outgo.

The loss of calcium in diabetic acidosis was shown by some experiments of Gerhardt and Schlesinger.[12] When the daily intake was 0.81 gm. calcium, and the diet was constant, a healthy man excreted 0.62 gm. calcium and a diabetic patient excreted 1.127 gm. calcium. The results obtained by von Limbeck,[13] Tenbaum[14] and von Moraczewski agree with those of van Ackeren,[15] Gerhardt and Schlesinger. Dengler[16] showed that the administration of calcium, but not of sodium, can stop for some time the loss of calcium in diabetic acidosis.

The work of Gaethgens, whose experiments were performed in 1866 in his student years, in which he makes the assertion that the calcium metabolism of diabetic patients who are not suffering from acidosis is normal, could not be corroborated and should be counted as an erroneous observation.

We wish here from the following observations of various scientists, working in totally different fields of research, to adduce some relation-

7. Towles: Am. Jour. Med. Sc., 1910, cxl, 127.
8. Von Noorden: Metabolism and Practical Medicine, 1907, iii, 600.
9. Mandel and Lusk: Deutsch. Arch. f. klin. Med., 1901, lxxxi, 472.
10. Gaethgens: Dissertation, Dorpat, 1866.
11. Kulz: Diabetes Mellitus, Jena, 1899, p. 430.
12. Gerhardt and Schlesinger: Exper. Arch., 1899, xlii, 83.
13. Von Limbeck: Ztschr. f. klin. Med., 1898, xxxiv, 439.
14. Tenbaum: Ztschr. f. Biol., 1898, xxxiii, 379.
15. Van Ackeren: Compare von Noorden's Lehrbuch der Pathologie des Stoffwechsels für Aerzte und Studirende, 1893, p. 416.
16. Dengler: Compare von Noorden's Metabolism and Practical Medicine, 1907, iii, 597.

ship existing between calcium metabolism and glycemia and glycosuria. We will consider the question from the following points of view:

(1) Relation of internal secretions to the control of calcium metabolism and carbohydrate metabolism; (2) Nutrition in pregnancy; lime and carbohydrate metabolism; (3) Infectious diseases characterized by derangement in lime metabolism and its effect on the glycemia; (4) Diabetes mellitus: fat metabolism, carbohydrate metabolism and lime requirements; (5) Experimental diabetes and its effect on calcium metabolism.

1. It is known that extirpation of the pancreas (von Mering) induces a marked disturbance in carbohydrate metabolism, with the elimination of large amounts of glucose in the urine. But the carbohydrate metabolism is not the only derangement of metabolism in the body. Falta and Whitney[17] in 1908 investigated the effects of resection of the pancreas in the dog on the lime metabolism, among other observations. They found a very marked increase in the outgo of all constituents, the increase affecting the minerals more than the protein distinction. The output of calcium was markedly increased as will be seen from Table 1.

TABLE 1.—Showing the Effect of Pancreatectomy on the Calcium Elimination in the Dog

Condition of Dog (fasting)	Date	CaO in Urine, Gm.
Normal	June 5	0.0175
Normal	June 6	0.0198
Normal	June 7	0.0246
Normal	June 8	0.0366
Pancreas removed	June 18	0.0124 (in 14 hrs.)
Pancreas removed	June 19	0.1522
Pancreas removed	June 20	0.0792
Pancreas removed	June 21	0.0885

In this case it seems, therefore, that the carbohydrate loss and the derangement in lime metabolism went hand in hand.

In a paper by Underhill and his collaborators we have another evidence of the simultaneous derangement of carbohydrate and calcium metabolism induced by a disturbance of the internal secretions. It is known from the work of McCallum and Voegtlin[18] that after parathyroidectomy there is an increased elimination of lime with a resulting deprivation of this element from the tissues and the blood. This

17. Falta and Whitney: Beitr. z. chem. Phys. u. Path., 1908, xi, 224.
18. McCallum and Voegtlin: Jour. Exper. Med., 1909, xi, 155.

deficiency induces a condition of tetany which can be cured by the administration of calcium lactate, etc. But not only does the resection of the parathyroids induce lime starvation. Underhill[19] and his collaborators found that there was a disturbance in the glycemia of his dogs, and they draw the following conclusions from their work:

(*a*) Hypoglycemia resulting from thyroparathyroidectomy is neither the cause nor the effect of the accompanying tetany; for although dextrose injections restore blood sugar content to normal, such injections have little influence on tetany. Moreover the condition of hypoglycemia precedes that of tetany. It is therefore suggested that the removal of the thyroid and parathyroids gives rise to two distinct effects, one being manifested upon the blood sugar regulating mechanism, causing hypoglycemia, the other acting upon the nervous system, producing tetany.

(*b*) Calcium appears to be intimately associated with both effects, for injections of calcium lactate will temporarily restore blood sugar to normal and also abolish tetany for a time.

(*c*) Calcium may play an important rôle in maintaining the equilibrium of the blood sugar regulating mechanism during normal life.

In the diseases of the pituitary gland, such as acromegaly, "it is remarkable how often it is associated with diabetes mellitus as a complication" (von Noorden[20]). Sir Edward Schäfer writes as follows on Acromegaly:

> There is often glycosuria . . . According to André Levi glycosuria occurs in from 30 to 50 per cent. of cases of acromegaly. As the case advances, it may be replaced by high degrees of sugar tolerance . . . It is interesting to note that in pregnancy also . . . glycosuria not infrequently occurs.†

In acromegaly there is a distinct disturbance of lime metabolism. Rubinraut,[21] Edsall and Miller,[22] Parhon,[23], Medigreceanu and Kristeller,[24] von Moraczewski,[25] and Bergeim, Stewart and Hawk[26] found a calcium retention. On the other hand, Tauszk and Vas[27] found an increased excretion of lime. Varying results were obtained by Franchini,[28] Schiff[29] and Oberndorfer,[30] It must be remembered that the

19. Underhill and Blatherwick: Jour. Biol. Chem., 1914, xix, 119.
20. Von Noorden: Metabolism and Practical Medicine, 1907, iii, 565.
21. Rubinraut: Dissertation, Zurich, 1912.
22. Edsall and Miller: Univ. Pennsylvania Med. Bull., 1903, xvi, 143.
23. Parhon: Cited by Medigreceanu and Kristeller.
24. Medigreceanu and Kristeller: Jour. Biol. Chem., 1911, ix, 109.
25. Von Moraczewski: Ztschr. f. klin. Med., 1901, xliii, 336.
26. Bergeim, Stewart and Hawk: Jour. Exper. Med., 1914, xx, 218.
27. Tauszk and Vas: Pest. med.-chir. Presse, 1899, xxxv, 193.
28. Franchini: Biochem. Zentralbl., Ref. 1904, iii, 522.
29. Schiff: Wien. klin. Wchnschr., 1897, xii, 277.
30. Oberndorfer: Ztschr. f. klin. Med., 1908, lxv, 6.

† Schäfer, Sir Edward: An Introduction to the Study of the Endocrin Glands, 1914, p. 66.

cases of acromegaly studied were during different periods of the disease, and that some of them doubtlessly had no complicating glycosuria, so that the conflicting results can be easily explained.

2. Pregnancy is a condition in which marked metabolic changes go on. Hugounenq[31] studied the retention of minerals by the human fetus. The retention of minerals by the fetus is slight at first, but very active at the end. At birth the infant contains about 100 gm. of salts. During the last three months of gestation the fetus acquires twice as much mineral matter as previously.

It is generally known that calcium is lost by the mother during pregnancy. The results of Ver Eecke,[32] Jagerroos,[33] Michel,[34] Schkarin,[35] Hoffstrom,[36] and others demonstrate this fact. Marquis[37] found a normal physiologic decalcification in pregnancy, which if varied to excess will develop into an osteomalacic condition. He concludes that the decalcification in pregnancy is probably due to some disturbance in ovarian, suprarenal or similar functioning, with a predisposition afforded by frequently repeated pregnancies and deficiency of lime in the food. This marked loss of lime in the parturient woman induces a disturbance in the carbohydrate metabolism.

Geelmuyden[38] comments on the connection between the functioning of the female internal genital organs and carbohydrate metabolism, saying that glycosuria develops regularly in about 10 or 12 per cent. of all pregnancies. Some have encountered it in 40 per cent. Usually lactose is the sugar in the urine in this benign pregnancy glycosuria, but it may be glucose or both. The proportion of sugar in the urine may be so large as to suggest severe diabetes with acidosis. Some differential points are its onset first during the pregnancy, its independence of carbohydrates in the diet, and the absence of polyuria and excessive thirst. Geelmuyden has known instances of these latter symptoms, polyuria, thirst and pruritus, occurring with unmistakable pregnancy glycosuria.

3. There are certain diseases which are characterized by decalcification, as for example in pneumonia and tuberculosis. In tuberculosis the demineralization is so marked that a French school of physicians

31. Hugounenq: Compt. rend. Soc. de biol., 1899, li, 337.
32. Ver Eecke: Acad. Roy. de Med. de Belgique, 1900, xv, 1.
33. Jagerroos: Arch. f. Gynäk., 1902, lxvii, 517.
34. Michel: L'obstetrique, 1896, i, 140.
35. Schkarin: Monatsbl. f. Kinderh., 1910, ix, 65.
36. Hoffstrom: Arch. f. Physiol., 1903, xxiii, 326.
37. Marquis: L'Obstetrique, 1914, xxx, 561.
38. Geelmuyden: Norsk Mag. f. Laegevidensk., 1914, lxxv, 865.

have recommended lime therapy for tuberculosis (Ferrier,[39] Letulle,[40] Vanini,[41] Piettre,[42] Kahn.[43]

Hopkins[44] has found a constant hyperglycemia in pneumonia, tuberculosis and other conditions, so in these diseases, also, decalcification and decreased carbohydrate tolerance go hand in hand.

4. Lipemia and acidosis, which are such constantly concurring conditions of diabetes mellitus, have a distinct relationship to calcium metabolism.

Klemperer[45] observed that in diabetic mellitus the blood contains much cholesterol and lecithin, which originate from the subcutaneous fat. The fat of the viscera is unchanged. The lipins enter the blood because of the breakup of the body cells. Once in the blood, they attempt to regenerate the impaired cells. In brief, diabetic lipemia represents a mobilization of the cell lipins to form new cells.

Drennan[46] drew the following conclusions as to the pathogenesis of diabetic lipemia:

(*a*) The lipemia of diabetes mellitus is due to the abstraction of calcium salts from the lipoid circulating in the blood.

(*b*) This abstraction is an attempt on the part of nature to neutralize the organic acid which results from the imperfect oxidation of the sugar in the body, fat in the blood being the lesser of the two evils. Fat embolism may result in the lungs, but may exist quite extensively without causing serious symptoms.

In acidosis there is a marked mobilization of lime from the body. All authors agree that the calcium deficiency is marked in cases of increased acid production in the body due to incomplete or improper oxidation of fats.

5. Experimental glycosuria and experimental diabetes can be induced in several ways. It is known that adrenalin, phlorhizin, caffein, etc., will cause glycosuria. Their method of action is not known. In the case of phlorhizin diabetes, the effect, as has been proved by Zuntz, is local on the kidney. In the case of caffein and adrenalin it may be central. In all of these conditions a simultaneous derangement in lime metabolism is present. Salant and Kahn[47] in 1913 showed that the administration of calcium to rabbits suffering from caffein diabetes caused a cessation of the glycosuria; and if the animal was fortified

39. Ferrier: Compt. rend Soc. de biol., 1909, xlix, 464.
40. Letulle: Presse méd., 1909, xvii, 212.
41. Vanini: Bull. d. sci. méd., 1908, No. 8.
42. Piettre: Compt. rend. Acad. d. sc., 1909, cxlviii, 954.
43. Kahn: Biochem. Bull., 1912, ii, 87; Med. Rec., New York, 1914, June.
44. Hopkins: Am. Jour. Med. Sc., 1915, cxlix, 115.
45. Klemperer: Deutsch. med. Wchnschr., 1912, October 10.
46. Drennan: Med. Rec., New York, May 7, 1910.
47. Salant and Kahn: Jour. Pharmacol. and Exper. Therap., 1913, v, 535.

with lime before the caffein administration, the glycosuria was never apparent. Similar results were synchronously reported by workers in Germany on adrenalin and nicotin diabetes. Furthermore, Jacoby and Rosenfeld[48] have reported that the administration of calcium lactate to dogs has an immediate effect upon phlorhizin diabetes, the excretion of sugar and acetone falling rapidly to almost zero. The decrease in urinary sugar was accompanied by a parallel decrease in the blood sugar. Thus the sugar formation by phlorhizin is hindered by the lime salts.

Substances which abstract lime from the tissues will induce in certain cases a glycosuria. This is true of citrates and tartrates. We have observed that rabbits will often develop glycosuria upon the administration of tartrates.

Bock and Hoffmann observed that they could induce a glycosuria by injecting large quantities of sodium chlorid. Martin Fischer demonstrated that this glycosuria can be arrested by the administration of calcium chlorid solution.

Surgical production of melituria by puncturing the floor of the fourth ventricle or by extirpation of the pancreas will induce, not only a derangement of the carbohydrate metabolism, but also a violent mobilization of the lime salts.

Hagiwara[49] has recently reported that he found extensive deposition of calcium in the liver of a man who died in diabetic coma. He could not explain this condition. The calcium in the liver was in the form of soap.

The important rôle that calcium plays in the human economy is well discussed by G. Delgado Palacios.[50] He found that all diabetics suffer from a calcariuria and lipaciduria.

EXPERIMENTAL

The lime metabolism of five diabetic patients was studied.[51] The patients were kept on a Folin diet, no sugar being given, and portions of the mixed diet were taken to the laboratory for analysis. The urine and feces were collected daily and analyzed. The experiments were conducted for nine days. The patients were in the mild stages of diabetes, none of them suffering from any discomfort. There was no acidosis, no ulceration, no pruritus. The glycosuria varied in the different cases from 1.5 to 2.7 per cent.

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48. Jacoby and Rosenfeld: Biochem. Ztschr., 1915, lxix, 155.
49. Hagiwara: Centralbl. f. allg. Path. u. path. Anat., 1915, xxvi, 481.
50. Palacios: Chimie pathologique Tropicale de la Région Atlantique, Caracas, Venezuela, 1914. Biochemical Bulletin, 1916, v, 78.
51. These investigations were conducted in the Beth Israel Hospital Chemical Laboratory, New York City, in collaboration with Jacob Hoffmann. A preliminary report was made in the Biochemical Bulletin, 1915, iv, 213.

It was found that the patients on this diet constantly lost lime from their bodies. In certain instances this loss of calcium was marked, in others it was only slight, but the negative calcium balance was definite at all times. Table 2 shows the daily loss of calcium of each patient for a period of nine days.

TABLE 2.—Intake and Output of Calcium Oxid by Diabetic Patients *

Case No.		Day								
		1	2	3	4	5	6	7	8	9
1	Intake.....	1.785	1.826	1.941	2.072	1.785	1.907	1.625	1.789	1.847
	Output.....	1.854	1.878	1.977	2.143	1.795	2.044	1.893	1.937	2.094
	Loss.....	0.069	0.052	0.036	0.071	0.011	0.137	0.278	0.148	0.247
2	Intake.....	1.989	1.937	1.874	1.925	2.130	2.107	2.006	1.994	1.895
	Output.....	2.167	2.027	1.948	2.182	2.229	2.234	2.139	2.276	2.227
	Loss.....	0.178	0.090	0.074	0.256	0.099	0.127	0.133	0.282	0.332
3	Intake.....	2.017	2.172	1.987	1.874	1.975	1.981	1.957	1.944	1.927
	Output.....	2.245	2.258	2.187	1.939	2.187	2.110	2.064	2.163	2.126
	Loss.....	0.228	0.186	0.200	0.065	0.212	0.129	0.107	0.219	0.099
4	Intake.....	1.756	1.728	1.925	1.834	1.955	1.974	1.873	1.977	1.926
	Output.....	1.847	1.847	1.976	2.006	2.139	2.177	2.065	2.164	2.165
	Loss.....	0.118	0.119	0.051	0.172	0.184	0.203	0.192	0.187	0.239
5	Intake.....	2.374	2.177	2.250	2.304	2.572	2.714	2.394	2.424	2.342
	Output.....	2.527	2.264	2.376	2.572	2.837	2.907	2.567	2.637	2.561
	Loss.....	0.153	0.087	0.126	0.268	0.265	0.193	0.173	0.213	0.219

* The lime was determined by the McCrudden method.

In a number of cases in another series we endeavored to remedy this lime deficiency and to observe the effect of the lime administration on the glycosuria and the glycemia of the diabetic patients. The method of procedure was as follows:

The patients were kept on a standard diet for a period of three days, during which the urine was collected and the glucose analyzed daily, the amount of glycemia being also determined. On the same diet the patient was injected intravenously with varying amounts of an eighth-molecular solution of calcium chlorid in physiologic saline. The glycosuria and glycemia were then determined to observe the effect of the treatment. We shall describe our results in detail:

Case 1.—S. D., a German Jewess, aged 40, married, and having four children, all in good health, had a negative family history.

She had had the usual diseases of childhood, but no other illnesses or operations. She had suffered an injury to the left cornea in 1900, which left an

opacity. Otherwise her history was negative. Her habits were regular and normal.

Her present illness dates from 1912, when she weighed 140 pounds, and since which time the patient has been aware of diabetic conditions. She has been losing weight constantly, has had polydypsia and polyuria frequently and also pruritus vulvae. These symptoms existed at the commencement of treatment.

On physical examination her weight was found to be 110 pounds, her general condition fair, but showing evidences of emaciation. Her heart and lungs were negative, liver slightly enlarged, from the sixth intercostal space to three fingers below the free border of the ribs. There was slight epigastric tenderness, but no abdominal masses. The neurologic status was normal. The blood pressure (Tycos) was systolic 145 millimeters of mercury, and diastolic auscultatory 80.

During 1913 the patient had recorded urinalyses of 1.5, 0.3, 4, 2.5, 0.9 and 4 per cent. of sugar in single specimens of urine. No acetone bodies were present.

During 1914 the urine contained 6 and 5 per cent. in twenty-four-hour specimens.

In February, 1915, a twenty-four-hour specimen showed 6 per cent. and in May, 5 per cent.

On May 15, 1915, the patient was put on a constant diet, which was maintained throughout the entire time of observation. The diet consisted of the following ingredients:

Breakfast: Two eggs, one slice of bread and much butter, one glass of tea with cream, water as much as desired. Dinner: Cooked meat with green vegetables, one slice of bread and much butter, cheese or two eggs, whisky one-half ounce, one glass of tea with cream but no sugar. Supper: Meat soup, cooked meat with green vegetables, cheese or two eggs, one slice of bread and much butter, whisky one-half ounce, one glass tea with cream but no sugar.

On May 18 about 5 c.c. of blood were drawn from the medium basilic vein for analysis, and an intravenous injection of 25 c.c. of the calcium solution in normal saline was given. There were no immediate effects, but for several hours the patient felt very weak. The urine was collected, beginning with an empty bladder at the time of injection.

On May 21 there was made an intravenous injection of 30 c.c. of the calcium solution after a few cubic centimeters of the blood had been drawn for examination. There were no immediate effects, except that the blood pressure fell from that previously mentioned to a systolic of 125 and diastolic of 70 millimeters of mercury. For several hours following the injection the patient said she felt weaker than normal.

On May 30 an intravenous injection of 15 c.c. of calcium solution was made after a little blood had been drawn for examination

On June 16 an intravenous injection of 40 c.c. of calcium solution was made. The patient felt great general discomfort and weakness. The pulse remained unchanged and the patient had no local reaction.

On June 18 an intravenous injection of 45 c.c. of calcium solution was made. The blood pressure fell to systolic 120, diastolic 70 directly after injection.

On June 20 there was made an intravenous injection of 50 c.c. of calcium solution. When 15 c.c. had been injected, patient suddenly flushed, but became very pale as the injection continued. But the pulse remained strong and regular, and patient left the office after several minutes. There occurred a slight local reaction as a result of a few drops which entered subcutaneously, with very severe pain for several hours. This was relieved by a wet dressing.

On June 22 another intravenous injection of 50 c.c. of calcium solution was made. At the outset there was flushing of the face, but this was followed by pallor. The pulse was good, though the patient felt very weak. No immediate effects followed. For several days the patient had localized swelling at the site of the injection. About an hour after the injection the patient had severe

neuralgic pain in the occipital region, with a sense of constriction about the waist.

On June 24 was made an intravenous injection 30 c.c. of calcium solution of which about 15 c.c. were subcutaneous. At the time there was but little pain, but after two hours there developed the brawny condition previously described, which lasted a considerable length of time.

During the period patient was receiving injections the epigastric sensations of oppression were relieved, but on July 13 they returned, and the weakness was quite troublesome.

It is well here to enumerate some of the by effects produced by the injection of the lime solution. The usual effect was a sudden flushing of the face when about 15 c.c. were injected, followed by marked pallor

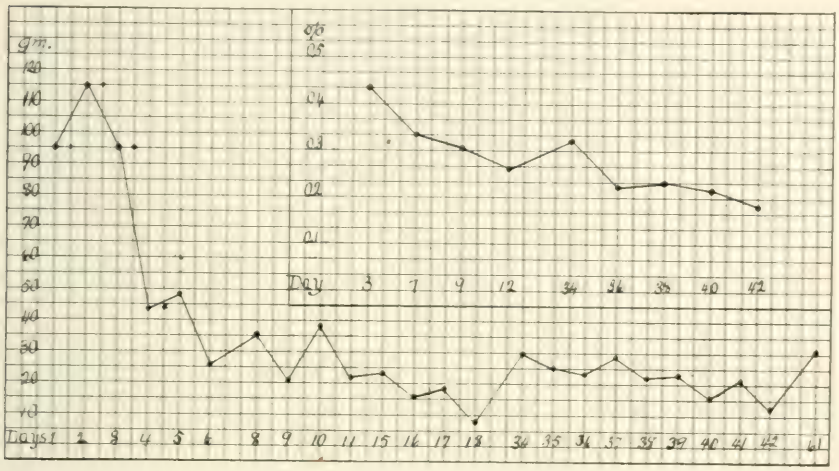

Fig. 1.—The smaller chart shows the fall in hyperglycemia as a result of the calcium solution injections. The vertical column of figures indicates the percentage of blood glucose; the horizonal line the time in days. The larger chart shows the result of the injections on glycosuria. The vertical column of figures indicates the diabetic glucose in grams per day; the horizontal the time in days (S. D., Case 1).

and a feeling of weakness when the injection was continued. After about one hour the weakness in several cases was marked and the patient had to remain in bed for a few hours, complaining of general pains in the muscles. The blood pressure fell immediately after the injection, both systolic and diastolic, with a fall also in the pulse pressure.

In one case, when 15 c.c. of the solution were injected for the first time, the patient said that she "felt hot all over," and then "cold all over," with flushing and pallor respectively, until 30 c.c. were introduced. After thirty minutes the patient felt extremely faint, was pale, had a cold perspiration and for a while was practically unconscious.

She continued in a profuse cold perspiration, and complained of severe aching pain in the arms, chest, back, and legs, and of faintness. The heart sounds were very weak, respiration deep and sighing, marked pallor and cold extremities, with all the signs of collapse. After several hours with hot drink, elevation of the foot of the bed, hot blankets, color and normal general condition returned.

In another instance there was a sensation of fluid "coursing through the brain" for a short period after the injection.

The local effects of subcutaneous extravasation of some of the fluid are at times severe. In one patient in whom 15 c.c. were injected subcutaneously in the right elbow region just beside the vein, there was little pain at the time, but after two hours there occurred marked edema of the anterior aspect of the whole right arm extending from the elbow to the deltoid region. Superficially there appeared red blotches as if the skin were becoming necrosed from pressure. It was freely movable, however, over the very hard and brawny edema. The hardness of the edema was most unusual, as it did not even pit on pressure. At the end of one week the extent of the infiltration began to diminish, but the firmness of consistency of the subcutaneous tissues remained unchanged in the parts still involved. After two more weeks there still was a small area of subcutaneous hardening in the region of the right elbow, which did not pit on pressure and was slightly tender. Finally, however, the arm returned to its normal appearance.

This patient, S. D., was excreting from 95 to 116 gm. of glucose daily. On the third day she was injected with 25 c.c. of calcium solution. The excretion of glucose fell to 43.75 gm. on the fourth day. On the fifth day she excreted 48.60 gm. glucose. She now received another injection of 30 c.c. calcium solution. On the sixth day she excreted 26.83 gm. glucose, and on the seventh day the excretion was 37.92 gm. Again a dose of 30 c.c. calcium solution was administered intravenously. On the day following she had 20.12 gm. glucose, on the ninth day 39.37 gm., on the tenth day 22.60 gm., and on the eleventh day 24.37 gm. glucose. The calcium solution was again injected—15 c.c. On the day following the patient excreted 15.75 gm. glucose, on the thirteenth day 17.87 gm., on the fourteenth day 13.60 gm.

The glycemia was estimated four times, in each case on the blood sample previous to the calcium administration. The hyperglycemia fell from 0.44 per cent. to 0.34 to 0.31 and to 0.27 per cent.

A period of about three weeks was now allowed to elapse from May 30, 1915, to June 16, 1915, when the patient was again treated with the calcium solution. During this time the glycosuria had risen again to 2.6 per cent. and the glycemia to 0.305 per cent. The administration of calcium again had the marked effect of reducing the glycemia and glycosuria.

Table 3 will show the effect of the calcium on the glycosuria and glycemia.

TABLE 3.—Effect of Calcium Administration on the Glycosuria and Glycemia of Case 1 (S.D.)

Date	Urine, c.c.	Glucose		Glycemia, per Cent.	Remarks
		Per Cent.	Grams		
May 15	1,875	5.1	95.625	....	
16	2,050	5.7	116.85	....	
17	2,000	4.8	96.00	0.44	
18	1,750	2.5	43.75	....	Injection
19	1,800	2.7	48.60	....	
20	1,720	1.56	26.83	0.34	Injection
22	2,050	1.85	37.92	....	
23	1,750	1.15	20.12	0.31	Injection
24	1,575	2.5	39.37	....	
25	1,650	1.4	22.60	....	
29	1,875	1.3	24.37	0.27	Injection
30	1,750	0.9	15.75	....	
31	1,625	1.1	17.87	....	
June 1	1,700	0.8	13.60	....	
16	1,650	2.5	31.250	0.32	Injection
17	1,500	1.7	25.50	....	
18	1,625	1.5	24.375	0.22	Injection
19	1,750	1.7	29.750	....	
20	1,550	1.4	23.700	0.24	Injection
21	1,550	1.4	23.700	....	
22	1,500	1.1	16.500	0.22	Injection
23	1,875	1.2	22.500	....	
24	1,650	0.8	13.200	0.19	Injection
July 13	1,750	1.9	33.250	....	

The acetone "bodies" were never present in the urine.

Case 2.—S. K., a Russian woman, aged 39, had a family history which was negative for diabetes and tuberculosis.

She had had one curettage, but no illnesses except headaches and fainting sometimes. For two years she had had marked thirst, and one year ago she had been informed that she had diabetes. She had lost much weight despite her good appetite. She had had pruritus vulvae one year, which had become worse recently. Her bowels were constipated.

Physical examination showed her to be in good general condition, weighing 161 pounds. Her heart sounds were clear and normal, and her lungs showed no morbid indications. There was abdominal tenderness in the gallbladder region. The liver and spleen were not palpable. The neurologic status was normal. The blood pressure was systolic 108, diastolic 68.

Sept. 22, 1915, the patient was put on a strict and constant diet which was adhered to throughout the entire period of observation.

On September 25 an intravenous injection of 30 c.c. of the calcium solution was made. The sensation of heat followed by pallor and cold occurred, and the collapse described previously followed in about thirty minutes. The patient received 5 grains of caffein by mouth at this time, but the urine and blood were examined as usual.

On October 8 she felt much improved, itching was slight, and her weight had increased to 162½ pounds.

On October 25 a sample of blood was taken for examination, but as the cubital veins were very small and deep, the injections were not continued, but the daily administration by mouth of 30 grains of calcium chlorid was begun. On December 3 her weight remained practically unchanged, being 162 pounds.

In this case, following the injection of the calcium solution, the urine sugar and glycemia fell from 5.1 per cent. to 2.7 per cent., and from 0.037 to 0.025, respectively. Her reaction to the lime solution was such that it was deemed unadvisable to continue any intravenous administration in her case.

Case 3.—C. A. H., a married man, aged 53, referred to us by Dr. Joseph Heine of New York, had a negative family history. His past history showed no illnesses or operations, except that twelve years ago he had an attack of gout in a toe. For the past seventeen years he had drank about twenty glasses of beer daily. The patient recently has been taking six or seven drinks of whisky, several glasses of claret and several glasses of beer every night between 11 p. m. and 1 a. m., on an empty stomach. He denies venereal disease, and he does not smoke or chew.

For ten years the patient had had diabetes, marked polydypsia and polyuria, but a good appetite. Six years previously he had had sciatic neuritis, following which time he had had slight paresthesias in the feet. At that time the patient had lost 60 pounds in weight. He had had eczema on the legs one year before.

The patient ate at 12 m., then again at 6 p. m. each day. Between 11 p. m. and 1 a. m. regularly each day he drank the great amount of alcohol as mentioned before. The Wassermann test was negative.

Physical examination showed his general condition to be good. He weighed 186 pounds. His heart was regular with no murmurs. The second sounds at the base were not accentuated. The lungs were clear. Superficial band of capillaries quite marked on both sides of chest above the costal margin. The abdomen was protuberant. There were no ascites and no edema of the legs or feet.

Nov. 23, 1915, the patient was put on a constant diet, which was maintained throughout the entire time of observation, and which consisted of the following:

Breakfast: Three eggs, two slices of toast with butter, one whole grapefruit, one glass of tea with cream and saccharin, water ad libitum, sodium bicarbonate one teaspoonful. Dinner: Soup of meat or vegetables, meat, green vegetables, cream cheese, two rolls with butter, one glass of tea with cream. The patient drank seven whiskies daily from 11 p. m. to 1 a. m., and in addition, two glasses of claret and five glasses of beer.

On November 29 was made an intravenous injection of 15 c.c. calcium solution, with no general effects.

On December 2 another intravenous injection of 20 c.c. calcium solution was made, but there was no immediate effects except a sensation of circulation in the head.

December 5 an intravenous injection of 30 c.c. calcium solution was given. The patient at this time weighed 190 pounds.

On December 9 an intravenous injection of 40 c.c. calcium solution was given and on December 12 the patient said he felt much better. Since these injections were given the patient has been on a diet similar to the foregoing, and the urine has gradually diminished to about 70 ounces daily, and has now reached 0.6 per cent. sugar and the patient feels well. The patient's urine is now (May 17, 1916) entirely sugar free.

TABLE 4.—Effect of Calcium Administration on Glycosuria and Glycemia in Case 3 (C. A. H.)

Date	Urine, c.c.	Glucose		Glycemia, per Cent.	Remarks
		Per Cent.	Grams		
Nov. 25	2,875	4.54	130.52	.....	
26	3,025	4.30	130.07	.....	
27	3,275	4.23	128.53	0.427	
29	3,300	2.30	75.90	.....	Injection
30	3,300	2.70	89.10	.....	
Dec. 2	3,300	1.85	61.05	0.235	Injection
3	3,300	1.70	56.10	0.175	Injection
12	2,100	0.6	12.60	.....	

The next several cases will not be reported in such complete detail.

Case 4.—Mrs. C., who was referred to us by Dr. Zugsmith of Pittsburgh, a woman in easy circumstances, had been suffering from diabetes for a number of years. She was placed on a constant diet and a number of injections of a calcium solution were made. No untoward effects were noticed. The results we obtained in this case are given in Table 5.

TABLE 5.—Effect of Calcium Administration on Glycosuria and Glycemia in Case 4 (Mrs. C.)

Date	Urine, c.c.	Glucose		Glycemia, per Cent.	Remarks
		Per Cent.	Grams		
Oct. 6	1,785	3.2	57.12	....	
7	1,900	3.4	64.60	....	
8	1,850	1.2	22.20	0.23	Injection
9	1,570	1.4	21.98	....	
10	1,450	1.1	15.95	....	
11	1,580	1.7	26.86	....	
12	1,600	0.9	14.94	0.23	Injection
13	1,655	1.1	18.205	....	
14	1,470	0.8	11.56	....	
15	1,750	0.5	8.75	0.21	Injection
16	1,645	0.5	8.225	....	
17	1,720	0.6	10 32	....	
18	1,630	0.3	4.89	0.19	Injection
19	1,450	0.2	2.90	....	
20	1,430	0.8	11.64	....	
Nov. 18	1,450	1.1	15.95	....	

Case 5.—Mr. Y., a patient in the Western Pennsylvania Hospital, was suffering from glycosuria. On a number of days he excreted from 30 to 40 gm. of glucose daily. He received one injection of the calcium solution intravenously. The next day he had no glucose in the urine. He left the hospital at that time, and we do not know the course of the disease since the injection. No untoward effects were observed from the calcium administration.

Case 6.—Mr. B., a man 53 years of age, had been suffering from diabetes for a number of years. He was treated with calcium administrations. Table 6 shows the result of the intravenous injections of calcium solution.

TABLE 6.—Effect of Calcium Administration on Glycosuria and Glycemia in Case 6 (Mr. B.)

Date	Urine, c.c.	Glucose		Glycemia, per Cent.	Remarks
		Per Cent.	Grams		
June 1	2,250	4.7	103.75	....	
2	2,870	5.2	144.24	....	
3	2,650	5.1	135.15	....	
4	2,730	4.8	121.04	....	
5	1,890	3.4	64.26	0.43	Injection
6	1,850	3.5	64.75	....	
7	1,780	3.2	56.96	....	
8	1,920	3.7	71.04	....	
9	1,670	2.8	46.76	0.41	Injection
10	1,730	2.5	43.25	....	
11	1,480	2.7	39.96	....	
12	1,580	2.2	34.76	0.32	Injection
13	1,560	2.4	37.44	....	
14	1,620	2.5	40.50	....	
15	1,570	1.7	26.69	0.24	Injection
16	1,540	1.4	21.56	....	
17	1,790	1.5	25.85	....	

In a number of cases we endeavored to produce the calcium effect by means of the administration of calcium lactate or chlorid per os. The results that we have obtained are not so striking as those produced by intravenous administration of the calcium. We shall report our results by this method of therapy in a future communication.

In general, we may draw the following conclusions from our experiments:

1. The administration of calcium intravenously to diabetic patients causes a marked fall in the glucose excretion.
2. It induces a gradual decline in the glycemia of the patients.
3. The quantity of urine excreted is reduced.

4. Certain symptoms ascribable to the diabetes are relieved by this treatment.

5. Acetone, diacetic acid and beta-oxybutyric acid never developed in these cases.

We are continuing our work along these lines.

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FURTHER STUDIES IN THE INACTIVATION OF PEPSIN

THE EFFECTS OF VARIOUS SALTS AND ALKALINE SUBSTANCES *

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In a previous communication by one of us[1] it was demonstrated that sodium chlorid will prevent pepsin in aqueous solution from digesting protein. It was further pointed out that the inhibition of pepsin by sodium chlorid is permanent, that is, the subsequent addition of hydrochloric acid fails to reactivate the ferment. This phenomenon of pepsin inhibition may be prevented by dissolving the ferment in dilute hydrochloric acid.

The inactivation of pepsin by sodium chlorid suggested the desirability of studying the action of various other salts to ascertain, if possible, whether this phenomenon was specific or whether it was common to many salts. Before this was attempted, however, a somewhat more detailed quantitative study of the action of sodium chlorid itself was made. The results from this study are shown in Table 1. Here it was found that the inhibitory effect of sodium chlorid is a quantitative reaction, that is, inhibition diminishes with the concentration of salt present. For instance, a concentration of 2.5 per cent. causes practically complete inhibition of pepsin. Lesser concentrations cause only partial inhibition, while concentrations of less than 0.25 per cent. cause practically no inhibition at all. In fact, in concentrations of salt below 0.25 per cent. inhibition is not only absent but is supplanted by actual acceleration, that is, there is apparently an optimum concentration of sodium chlorid of about 0.1 per cent., at which point peptic digestion is greater than in the entire absence of salt.

Similar studies were made with various chlorids, namely, potassium, barium, strontium, ammonium, magnesium and iron. The results with these salts were all practically the same, the phenomenon of inhibition remaining a quantitative reaction with evidence of acceleration in high dilutions.

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* From the Morris Institute for Medical Research, Chicago.

* Read at the Eighth Annual Meeting of the American Society for the Advancement of Clinical Investigation, Washington, D. C., May 8, 1916.

1. Hamburger: The Archives Int. Med., 1915, xvi, 356.

In connection with the inhibiting effect of these various chlorids the thought was suggested that hydrochloric acid itself might have an inhibiting action at certain concentrations. We made, therefore, quantitative studies with varying strengths of hydrochloric acid, with results as shown in Table 2. Here it may be seen that hydrochloric acid in concentrations of from 0.7 to 0.9 per cent. causes almost complete inhi-

TABLE 1.—Quantitative Inhibition of Pepsin by Sodium Chlorid*

Tube	Pepsin in H_2O, 1 to 300.	5 per Cent. NaCl	Normal HCl	H_2O	Digestion	
					24 Hr.	44 Hr.
1	5 c.c.	5 c.c.	0.5 c.c.	0	0	Trace
2	5 c.c.	1 c.c.	0.5 c.c.	4	+	++
3	5 c.c.	0.5 c.c.	0.5 c.c.	4.5	+	++
4	5 c.c.	0.1 c.c.	0.5 c.c.	4.9	++	+++
5	5 c.c.	0 c.c.	0.5 c.c.	5	++	++++

* Sodium chlorid in high concentrations (2.5 per cent.) causes complete inhibition of pepsin dissolved in water (Tube 1). In less concentrations inhibition, while not complete, is still present as compared with control (Tube 5). In concentrations less than 0.25 per cent. (Tube 4) the inhibition is almost negligible.

TABLE 2.—Inhibition and Acceleration of Pepsin by Hydrochloric Acid*

Tube	Pepsin in H_2O, 1 to 300	Normal HCl	H_2O	Digestion 48 Hr.
1	4 c.c	2 c.c.	2 c.c	0
2	4 c.c.	1.5 c.c	2.5 c.c.	Trace
3	4 c.c.	1 c.c.	3 c.c.	+
4	4 c.c.	0.75 c.c.	3.25 c.c.	+
5	4 c.c.	0.5 c.c.	3.5 c.c.	++
6	4 c.c.	0.25 c.c.	3.75 c.c.	+++
7	4 c.c.	0.1 c.c	3.9 c.c.	++
8	4 c.c	0.05 c.c.	3.95 c.c.	+
9	4 c.c.	0 c.c	4 c.c.	0

* Hydrochloric acid in high concentrations (0.7 to 0.9 per cent.) inhibits peptic digestion almost entirely (Tubes 1 and 2). Concentrations of about 0.1 per cent. (Tube 6) is optimum concentration under given conditions; in lesser concentrations, digestion again diminishes.

bition of aqueous pepsin. We found, further, that there was an optimum concentration of 0.1 per cent. at which point peptic digestion is at its height under given conditions, while in lesser concentrations down to entire absence of acid, digestion is proportionately less. In other words, we found evidence of a quantitative chemical reaction with a changing curve of peptic digestion reaching its maximum at a definite point under given conditions of optimum concentration.

Inasmuch as our work thus far had shown the equality of the various chlorids tested, we determined to vary the acid portion of the salt, the metal portion remaining constant. We chose for investigation the acetate, the citrate, the phosphate, and the carbonate of sodium. The results from this series were extremely interesting, for while the citrate and acetate showed practically the same results as the chlorids, the phosphate and carbonate showed a much greater inhibition. Table 3 contains a quantitative study of sodium phosphate, showing complete inhibition of pepsin in dilutions up to 1 to 200 and partial inhibition in

TABLE 3.—INHIBITION OF PEPSIN BY SODIUM PHOSPHATE*

Tube	Pepsin in H_2O, 1 to 1,000	5 per Cent. Na_2HPO_4	Normal HCl	H_2O	Digestion		
					22 Hr.	46 Hr.	70 Hr.
1	5 c.c.	5 c.c.	0.5 c.c.	0	0	0	0
2	5 c.c.	4 c.c.	0.5 c.c.	1	0	0	0
3	5 c.c.	3 c.c.	0.5 c.c.	2	0	0	0
4	5 c.c.	2 c.c.	0.5 c.c.	3	0	0	0
5	5 c.c.	1 c.c.	0.5 c.c.	4	0	0	0
6	5 c.c.	0.8 c.c.	0.5 c.c.	4.2	0	Trace	Trace
7	5 c.c.	0.6 c.c.	0.5 c.c.	4.4	0	Trace	Trace
8	5 c.c.	0.4 c.c.	0.5 c.c.	4.6	0	Trace	+
9	5 c.c.	0.2 c.c.	0.5 c.c.	4.8	Trace	+	++
10	5 c.c.	0.1 c.c.	0.5 c.c.	4.9	+	++	+++
11	5 c.c.	0	0.5 c.c.	5	++	+++	++++
12	5 c.c.	5 c.c. NaCl	0.5 c.c.	0	0	Trace	+
13	5 c.c.	1 c.c. NaCl	0.5 c.c.	4	–	++	++
14	5 c.c.	5 c.c. $NaC_2H_3O_2$	0.5 c.c.	0	0	Trace	Trace
15	5 c.c.	1 c.c. $NaC_2H_3O_2$	0.5 c.c.	4	++	+++	+++

* Sodium phosphate in dilutions up to 1 to 200 (Tube 5) causes complete inhibition of peptic digestion. In higher dilutions up to 1 to 2,000 (Tube 10) produce partial inhibition, as compared with control (Tube 11). Inhibition of other sodium salts (chlorid and acetates) in the same dilution was practically absent (Tubes 13 and 15).

dilutions as high as 1 to 2,000. This inhibition in high dilutions is in marked contrast to the results obtained with the sodium chlorid, for complete inhibition could be demonstrated only in dilutions up to 1 to 40 and partial inhibition in 1 to 400. In other words, the inhibiting effect of the phosphate may be said to be five times that of the chlorid, acetate or citrate.

A variety of inorganic and organic salts and alkaline substances were now tested under similar conditions, either on aqueous pepsin or on gastric juice. In the studies on gastric juice we would emphasize that a new and important factor enters into the reaction, namely, the

hydrochloric acid of the gastric juice, for in all of the work thus far the inactivating action of the various salts was tested on aqueous pepsin, which, as was shown in the earlier work, could be entirely protected by the addition, first, of hydrochloric acid.

Table 4 shows the results of the action of a series of salts on pure gastric juice. The results from this table may be said in brief to be entirely a question of the neutralization of the hydrochloric acid of the juice and the ability of the various salts and alkaline substances to

TABLE 4.—Effect of Various Salts and Alkaline Substances on Gastric Juice*

Tube	1st Addition	2d Addition	3d Addition, Normal HCl	Digestion	
				24 Hr.	48 Hr.
1	1 c.c. gastric juice	1 c.c. 5% Na_2CO_3.....	5 c.c.	0	0
2	1 c.c. gastric juice	5 c.c. 5% Na_2CO_3.....	5 c.c.	0	0
3	1 c.c. gastric juice	1 c.c. 5% $Na_3C_6H_5O_7$..	5 c.c.	+	++
4	1 c.c. gastric juice	0.5 c.c. 5% $Na_3C_6H_5O_7$	5 c.c.	++	+++
5	1 c.c. gastric juice	1 c.c. 5% Na_2HPO_4....	5 c.c.	+	++
6	1 c.c. gastric juice	0.5 c.c. 5% Na_2HPO_4...	5 c.c.	++	++++
7	1 c.c. gastric juice	1 c.c. 5% $Mg(OH)_2$.....	5 c.c.	+	++
8	1 c.c. gastric juice	0.5 c.c. 5% $Mg(OH)_2$...	5 c.c	++	++++
9	1 c.c. gastric juice	1 c.c. 5% $MgCO_3$.....	5 c.c.	0	0
10	1 c.c. gastric juice	0.5 c.c. 5% $MgCO_3$.....	5 c.c.	+	+
11	1 c.c. gastric juice	1 c.c. 5% KI.....	5 c c.	Trace	+
12	1 c.c. gastric juice	0.5 c.c. 5% KI.....	5 c.c.	+	++
13	1 c.c. gastric juice	1 c.c. 5% $NaC_{26}H_{42}NO_8$.....	5 c.c.	Trace	++
14	1 c.c. gastric juice	0.5 c.c. 5% $NaC_{26}H_{42}NO_8$.....	5 c.c.	+	+++
15	1 c.c. gastric juice	1 c.c. 5% $FeCl_3$.....	5 c.c.	+	+
16	1 c.c. gastric juice	0.5 c.c. 5% $FeCl_3$.....	5 c.c.	+	+
17	1 c.c. gastric juice	Control.....	5 c.c.	++	++++

* Carbonates show most striking inhibition, sodium carbonate more than magnesium carbonate. The inhbition is probably due to the alkalinity and the ability to neutralize the free hydrochloric acid of the gastric juice.

cause complete or partial neutralization. From this view point, as was to be expected, the carbonates showed by far the greatest inhibiting action, the sodium carbonate more than the magnesium. From triple tests with each salt, three indicators being used, namely, phenolphthalein, methyl orange and dimethylamido-azobenzol, it could be demonstrated that in the tubes showing complete inhibition the degree of alkalinization had progressed the farthest. We conclude, therefore, that sodium carbonate is of maxium value among the salts used for producing complete neutralization or alkalinization of gastric juice.

Confirmatory evidence of this view may be found in the results obtained in Table 5. Here it may be seen that when only free hydrochloric acid is neutralized, and then subsequently activating hydrochloric acid added, peptic digestion is simply reduced; however, when total acidity is neutralized and subsequently activating hydrochloric acid added, peptic digestion is destroyed completely and permanently.

These results, therefore, show that in order to control peptic digestion completely and permanently, total acid must be completely neutralized; for if only *free* acid is neutralized peptic digestion is prevented only temporarily (during the period of such neutralization), inasmuch as the subsequent addition of hydrochloric acid suffices to reactivate a considerable portion of the ferment. Of course, if the neutralization of free acid can be maintained, which means, clinically, the neutralization of all free acid as soon as secreted, peptic digestion will be controlled entirely during this period.

TABLE 5.—Effects of Partial and Complete Neutralization of Gastric Juice*

Tube	1st Addition	2d Addition	3d Addition	Digestion
1	3 c.c. gastric juice	N/10 NaOH sufficient to neutralize free HCl	.....	0
2	3 c.c. gastric juice	N/10 NaOH sufficient to neutralize free HCl	N/10 HCl sufficient for peptic digestion	++
3	3 c.c. gastric juice	N/10 NaOH sufficient to neutralize total acidity	.....	0
4	3 c.c. gastric juice	N/10 NaOH sufficient to neutralize total acidity	N/10 HCl sufficient for peptic digestion	0
5	3 c.c. gastric juice	Control.....	.....	++++

* Neutralization of free acid only (Tube 2) does not completely destroy peptic activity. Neutralization however of total acidity (Tube 4) destroys pepsin completely and permanently.

COMMENT

Summarizing the results which this study has brought forth, we may say that the inactivation of pepsin by sodium chlorid is not a specific phenomenon, but may be duplicated by any of a series of inorganic and organic salts. Further, the phenomenon partakes of the nature of a quantitative reaction, higher concentrations causing complete inhibition, lesser concentrations causing partial inhibition, while minimal concentrations cause acceleration. Hydrochloric acid also may act as an inhibiting agent to pepsin, in concentrations varying between 0.7 and 0.9 per cent. Such concentrations are considerably higher than are present in human gastric juice and are considerably higher than the concentration of salts causing pepsin inactivation.

Carl Oppenheimer and others previously have called attention to the inhibition or destruction of pepsin by relatively strong concentrations of hydrochloric acid. With the exception of such strong alkalies as sodium carbonate, sodium hydroxid, magnesium carbonate and calcium hydroxid, sodium phosphate causes the inactivation of aqueous pepsin in dilutions far greater than any salt investigated. Sodium phosphate inhibits or destroys pepsin in dilution five times greater than that of sodium chlorid, sodium acetate or sodium citrate. While this inactivation of pepsin by sodium phosphates suggests the possibility of a specific action, it is likely that this result is due to the feeble alkalinity exhibited by this salt. As Langley pointed out originally, alkalies, such as sodium carbonate, sodium hydroxid, magnesium carbonate and calcium hydroxid, inhibit pepsin by virtue of their alkalinity (hydroxyl ion concentration). We believe that our results are to be explained by this same chemical reaction. Langley found that pepsin was extremely sensitive to alkalies. He pointed out that if one wishes to neutralize gastric juice without destroying the activity of most of the pepsin, one should add calcium carbonate and then a very weak alkali, such as sodium acetate or milk of lime.[2] We believe it probable, therefore, that the inhibition of pepsin, both by salts and alkaline substances, is one and the same phenomenon, namely, the phenomenon of hydroxyl ion concentration, causing inhibition.

From a clinical point of view the results from this work suggest, theoretically at least, the advisability of using sodium chlorid and sodium phosphate in addition to the usual alkaline substances in the treatment of diseases of the stomach in which the control of peptic digestion may be desired. Whether or not the addition of sodium chlorid and sodium phosphate will actually aid in such therapy can only be determined by the clinical use of these salts in a considerable number of cases. Likewise the problem of the amounts required to control peptic digestion will necessitate prolonged clinical usage. In this respect, of course, the laxative effect of large amounts of sodium phosphate must be taken into consideration, as well as any possible remote (kidney) effects of large amounts of sodium chlorid. At the present time such clinical studies are being made. At this time we wish merely to call attention to their use and to suggest that as a prophylactic measure to aid in the prevention of gastric and duodenal ulcer, as well as a therapeutic agent to promote the healing of chronic ulcer, sodium chlorid and sodium phosphate should be used in addition to the usually employed alkaline drug and dietary treatment. It may be further suggested that inasmuch as sodium carbonate, magnesium carbonate and calcium hydroxid offer the maximum neutralizing value, these substances be used in place or in addition to the alkalies usually used in gastro-intestinal therapy.

2. Quoted from Mathews' Text-Book of Physiological Chemistry.

CONCLUSIONS

1. The inactivation of pepsin by sodium chlorid is not a specific phenomenon, but may be duplicated by any of a series of inorganic and organic salts.

2. The inactivation of pepsin by sodium chlorid is a quantitative chemical reaction. Concentrations of 2.5 per cent. cause complete inhibition; concentrations of 0.25 per cent. cause little, if any, inhibition; concentrations of 0.1 per cent. cause acceleration.

3. Hydrochloric acid in concentrations from 0.7 to 0.9 per cent. acts as an inhibiting agent to pepsin.

4. Sodium phosphate in dilutions of 1 to 200 causes complete inhibition of pepsin and in dilutions of 1 to 2,000 it causes partial inhibition of pepsin. The inhibition of sodium phosphate may be said to be five times that of sodium chlorid and of most inorganic and organic salts, with the exception of the strong alkalies.

5. The inhibition of pepsin by various salts and alkaline substances is probably due to the hydroxyl ion concentration of the solutions used.

6. The inhibition of pepsin by sodium chlorid and sodium phosphate suggests the possibility of the clinical use of these salts in the prevention and cure of chronic gastric ulcer.

7. The strong neutralizing value of sodium carbonate, magnesium carbonate and calcium hydroxid suggests the possibility of their use under similar conditions.

THE RATE OF ABSORPTION OF VARIOUS DIGITALIS PREPARATIONS FROM THE GASTRO-INTESTINAL TRACT *

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It has been shown that alcohol present in the tincture of digitalis delays the absorption of the active principles when this preparation is injected subcutaneously into guinea-pigs.[1] It seemed possible that the same delay in absorption might occur when the tincture was given orally, and this possibility is strengthened by the observations of Ryan,[2] who found that the absorption of strychnin from the stomach was delayed by the presence of alcohol, and those of Sollmann,[3] showing that alcohol delays the absorption of phenol from the alimentary tract. This is a point of some practical importance, for the delay in absorption not only delays the beginning of the desired digitalis action, but also allows a longer time for the digestive juices to act on the glucosids, causing, according to Hale,[4] more or less destruction of these latter.

Obviously, the most satisfactory way to determine the rate of absorption of a drug from the alimentary tract is to note the lapse of time between the oral administration of the drug in question and the appearance of definite symptoms which must be attributed to this drug. In investigating the rate of absorption of several digitalis preparations Cow[5] employed a method based on this principle. He used decerebrate cats, but instead of introducing the drug into the stomach, he injected it into the lumen of the small intestine and observed any subsequent change in the blood pressure. It would seem that there are two objections that can be advanced against this: first, the animals were deeply anesthetized, to be then operated on; and, second, the drug did not pass through the stomach, and this might have a decided influence on the results. Gottlieb[6] investigating the rate of absorption

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* From the Department of Pharmacology, Medical College of Virginia, Richmond, Va.

1. Haskell: Jour. Am. Pharm. Assn., 1913, ii, 830.
2. Ryan: Jour. Pharmacol. and Exper. Therap., 1912-1913, iv, 43.
3. Sollmann, Hanzlik and Pilcher: Jour. Pharmacol. and Exper. Therap., 1909-1910, i, 409.
4. Hale: Jour. Am. Med. Assn., 1911, lvii, 1515.
5. Cow: Biochem. Jour., 1911-1912, vi, 219.
6. Gottlieb and Ogawa: München. med. Wchnschr., 1912, lix, 2265.

of digipuratum and of powdered digitalis leaf, placed the preparations in the small intestine, and after the lapse of a given length of time, determined the amount of digitoxin remaining. The same objection might be urged against this injection site as was brought forward in regard to Cow's experiments, and, in addition, it is not generally believed that the determination of the so-called digitoxin by Keller's method is a procedure to be relied on.

In our first experiments the attempt was made to secure evidence of absorption after the oral administration of digitalis to anesthetized dogs, a constant record of carotid blood pressure being taken over periods of several hours. Irrespective of the digitalis preparation used, however, or the size of the dose, no evidence of absorption could be seen, even when the observations were continued over three hours.

It has been shown by Hatcher[7] that the seat of the emetic action of digitalis is central and not due to local irritation of the stomach. Therefore, emesis after the oral administration of a digitalis preparation indicates that absorption has occurred. Bearing this in mind, we gave a series of cats digitalis leaf, or infusion or tincture made from this leaf. The leaf was used in the form of a No. 60 powder; the tincture was made according to the official method. The infusion was made by placing the powdered leaf in a flask and adding boiling water in the proportion of about 90 c.c. for each 3 gm. of leaf. The flask was wrapped up and, in the first experiments, allowed to stand exactly three hours, in the later experiments, exactly four hours. The contents of the flask were then poured on a cloth filter, the leaf pressed, and water added through the filter until the finished infusion represented thirty grams of leaf to the liter. The tincture was tested on frogs and guinea-pigs at the time of its percolation, and each sample of infusion was tested in the same manner when made. No infusion over twenty-four hours old was used. Tincture and infusion assayed alike by the two methods.

All the animals received the drug by mouth. The powdered leaf was suspended in tap water and washed down with a small amount of water; the tincture was given as such, and was washed down with about an equal amount of water, except in three instances, in which the alcohol was evaporated off. The infusion was administered in an unchanged form. The results of these experiments are given in Table 1.

The result of these experiments would indicate that the infusion is absorbed more slowly than is the tincture. The experiments with the leaf are too few in number to permit of drawing conclusions for that preparation. When a dose of the infusion corresponding to 400 mg.

7. Hatcher and Eggleston: Jour. Pharmacol. and Exper. Therap., 1912-1913, iv, 113.

of leaf per kilogram cat was given to two cats, the average lapse of time before emesis was 267 minutes; when a similar dose of tincture was given to three other cats, the average lapse of time was 36.3 minutes. When the infusion dose was increased to 600 mg., 136.5 minutes elapsed as the average of two cats; while, with a corresponding dose of the tincture, one cat succumbed to the poisoning in 91 minutes without vomiting, the other vomited in 32 minutes after receiving the drug. A dose of the tincture corresponding to 300 mg. of leaf administered to two cats caused emesis in the average time of 37.5 minutes.

TABLE 1.—Effect of Digitalis Preparations Administered to Cats

Preparation	Mg. Leaf per Kg. Cat	Time Before Emesis, Min.
Leaf	100	27
Leaf	300	78
Leaf	300	71
Infusion	200	No emesis
Infusion	300	175
Infusion	400	203
Infusion	400	331
Infusion	500	58
Infusion	600	150
Infusion	600	123
Tincture	100	55
Tincture	200	13
Tincture	300	18
Tincture	300	57
Tincture	400	26
Tincture	400	40
Tincture	400	43
Tincture	500	12
Tincture	600	32
Tincture	600*	...

* Death in 91 minutes without emesis.

The rate of absorption of various digitalis bodies from the gastro-intestinal tract has been investigated in Hatcher's laboratory,[8] and it seemed desirable that the results given in Table 1 should be verified by the procedure that Hatcher has found so suitable for studying the rate of absorption from the alimentary tract of lower animals. This method is carried out on cats, a definite dose of the drug being given by mouth, and after the lapse of a suitable length of time a solution

8. Hatcher and Eggleston: Jour. Am. Med. Assn., 1914, lxiii, 468, 469.

of the same or a similar drug is gradually injected intravenously until the death of the animal occurs. Since the lethal dose for cats can be quite accurately determined with the digitalis bodies, it is obvious that the difference between the average lethal dose of the preparation in question and that actually required to kill an animal that has previously received an oral dose represents the amount of drug that has been absorbed from the stomach or intestines.

In carrying out our experiments according to this method, a tincture was made from digitalis leaf according to the official process, save that a No. 40 powder was used. This tincture was placed in a cork-stoppered pint amber bottle and used throughout the experiments, no assay being made after the original test, when it was found that a dose of this tincture corresponding to 100 mg. per kilogram cat was required to cause the death of the animals. The infusion was also made from the leaf in the form of a No. 40 powder. It was found, on using the process previously described, except that the water and leaf were allowed to remain in contact for exactly one hour, the finished infusion representing 20 gm. of the leaf to the liter, or, in other words, a 2 per cent. infusion, that infusion and tincture were of the same strength, figured on the basis of leaf represented. That is, 5 c.c. of a 2 per cent. infusion possessed the same amount of toxicity for cats as 1 c.c. of the 10 per cent. tincture. Hatcher and Eggleston[9] have recently shown that even the infusion does not deteriorate very rapidly, but it was deemed safer to use no infusion over twenty-four hours old.

The question arises as to the amount of absorption after the cats have been etherized. Necessarily, a considerable amount of time is taken up with the operative procedures and with the gradual intravenous injection. It has already been pointed out that dogs anesthetized with morphin-ether do not seem to absorb digitalis administered orally, and it is possible that with cats also absorption is largely inhibited after the induction of ether anesthesia. After placing the animals on the board and inserting the vein cannula, the attempt was made to avoid the further use of ether, but it was found that a small amount was required to keep the animals quiet. Frequently, the cats vomited, and if this occurred soon after the administration of the drug, it doubtless served to remove a portion of the dose that otherwise would have been absorbed and would have contributed to the lethal effect. In view of these facts, note was made of the time of oral administration, time of beginning ether, occurrence of emesis, and time of death. Some of the cats were starved twenty-four hours before use, others were allowed food, so the presence or absence of food in the stomach is also recorded. The results of these experiments are given in Table 2.

9. Hatcher and Eggleston: Jour. Am. Med. Assn., 1915, lxv, 1902.

TABLE 2.—Absorption of Tincture and Infusion by Cats

Sex	Weight, Gm.	Mg. Leaf per Kg. Cat	Ether Started, Min.	Emesis, Min.	Died, Min.	Stomach	Oral Dose Absorbed, %
Infusion:							
F.	2,300	100	42	0	117	Empty	1.3
M.	2,100	100	49	0	116	Food	4.5
F.	1,700	300	42	0	110	Food	10.8
M.	3,200	300	29	0	102	Empty	8.5
M.	3,300	300	31	50	132	Empty	0
M.	3,560	300	26	71	144	Empty	0
F.	1,660	300	24	66	142	Food	0
M.	2,570	300	28	97	102	Empty	0
F.	1,950	300	32	0	97	Empty	0
F.	1,265	300	20	40	90	Empty	0
M.	3,200	300	196	223	225	Food	9.8
F.	1,925	300	182	240	268	Food	3.9
Tincture:							
M.	2,370	300	25	57	130	Food	25
F.	2,430	300	22	65	87	Empty	12.6
F.	2,610	300	28	66	118	Empty	12.9
M	3,175	300	30	75	140	Empty	15.0
M.	2,790	300	24	102	103	Empty	13.6
M.	1,810	400	16	0	73	Food	0
M.	2,210	400	20	33	82	Food	2.4
F.	2,500	400	54	41	142	Empty	7.8
M.	3,180	400	40	38	75	Empty	8.2
F.	2,610	400	28	66	118	Empty	9.7
M.	2,790	400	24	103	103	Empty	10.2
M.	3,175	400	30	75	140	Empty	10.8
F.	3,400	400	21	16	86	Empty	11.3
F.	2,763	400	20	0	140	Empty	12.8
F.	1,310	400	20	0	94	Empty	13.7

It is evident from Table 2, that here also the rate of absorption of the tincture is much more rapid than is the case with the infusion. Six animals with empty stomachs received a dose of infusion equivalent to 300 mg. of leaf per kilogram of body weight, and after an average lapse of 111 minutes, only a little more than 1 per cent. of the dose administered was absorbed. Four cats with empty stomachs received a similar dose of tincture, and after the lapse of 112 minutes as an average, it is seen that over 13 per cent. of the dose had been absorbed. When the dose of tincture was increased to 400 mg., the percentage of absorption decreased somewhat, falling to about 9 per cent. As the

result of all the infusion experiments, an average absorption of 3.2 per cent. occurred; as the result of all the tincture experiments, an average of 9.5 per cent. The average lapse of time for the infusion animals was 137 minutes; for the tincture animals, 109 minutes.

It has been found that it is the presence of alcohol that delays absorption of digitalis after subcutaneous administration. Could it be that the alcohol had the reverse effect when the preparation is administered orally, or is the more rapid absorption of the tincture from the alimentary tract to be explained by the fact that it is a more concentrated preparation? In order to determine whether either of these factors exerted an influence, a portion of the tincture was evaporated on a water bath to a semisolid consistency and then suspended in tap-water to make a 2 per cent. solution, being, therefore, free from alcohol and having the same bulk as the infusion. This modified preparation was given to four cats with the results as shown in Table 3.

TABLE 3.—Absorption of Aqueous Suspension of Tincture Residue by Cats

Sex	Weight, Gm.	Mg.-Leaf per Kg. Cat	Ether Started, Min.	Emesis, Min.	Died, Min.	Stomach	Oral Dose Absorbed, %
M.	2,370	300	25	57	130	Food	2.3
F.	2,430	300	22	65	87	Empty	12.6
F.	26,100	300	28	66	118	Empty	12.9
M.	3,175	300	30	75	140	Empty	15

From these four experiments it is seen that the removal of the alcohol from the tincture and the increase in the bulk of the fluid has no influence on the rate of absorption. The average absorption was 10.9 per cent. of the administered dose, as against 9.5 per cent. in the series of animals receiving the ordinary alcoholic tincture. It would seem, therefore, that some constituent present in the infusion inhibits to a certain extent the absorption from the gastrointestinal tract of cats. Whether this occurs in man to an extent sufficient to play an important rôle is to be determined by clinical experimentation. From his clinical observations Eggleston[10] concludes that there is little or no difference in the action of the infusion and the tincture, but possibly more careful attention to the rate of absorption may reveal differences of considerable degree.

There are several special digitalis preparations on the market, possessing, according to the claims of their exploiters, numerous advantages over the galenical preparations. It has been shown that many

10. Eggleston: The Archives Int. Med., 1915, xvi, 1.

of these claims arise rather from a pleasing optimism of the manufacturers than from the ground of experimental fact, and, taking everything into consideration, we can see but few, if any, reasons for preferring them to the official preparations of suitable strength. Among other claims, it has been stated that some of these special preparations are more readily absorbed than are the official preparations. Aside from the experiments of Gottlieb that have already been mentioned, it does not seem that this question has been investigated by the exploiters of these preparations. To determine whether the rate of absorption really differed from that of the official preparations, samples of digipuratum, digalen, and digipoten were secured either from jobbers or retail druggists. These samples were first assayed by the cat method, and the rate of absorption after oral administration to cats was determined as in the preceding experiments.

The sample of digipuratum assayed by the cat method was found to possess a high degree of activity, the average lethal dose being 88 mg. per kilogram body weight. The tincture made in the laboratory from selected leaf and used in the preceding experiments, assayed in the same way, required a dose equivalent to 100 mg. leaf per kilogram body weight. The digalen sample was found much inferior in strength, the average dose being 428 mg. per kilogram. It is evident that this preparation is much weaker than a good sample of tincture, which is in agreement with previous assays of digalen by Hale[11] and by Hatcher.[12] The sample of digipoten also seemed of good strength, the lethal dose being 91 mg. per kilogram body weight. It was noticed, however, with this last preparation, that the death of most of the cats was atypical. A single blood pressure and respiration record was taken from a dog being poisoned with digipoten, and it was found that a gradual rise of pressure and slowing of the heart beat occurred, while the respiration, first stimulated in a decided manner and then depressed, continued a short while after the pressure had fallen to zero and the heart beat could no longer be detected. Apparently the preparation possesses the true digitalis action, but, from the manner of death of the cats, it would be necessary to investigate this more fully.

The results with digipuratum are given in Table 4.

It is plainly evident from these six experiments that digipuratum is absorbed less rapidly than is the tincture. When the dose of 300 mg. per kilogram body weight was given orally to six cats, at the end of an average of 161 minutes, an average absorption of about 5 per cent. of this dose had occurred; while with a similar dose of the tincture, after the lapse of an average of 112 minutes, an average absorption of about 13 per cent. had occurred. The sample of digipuratum is some-

11. Hale: Bull. Hyg. Lab., U. S. P. H. S., No. 74.
12. Hatcher: Jour. Am. Med. Assn., lviii, 921.

what stronger than was the tincture, but this does not nearly compensate for the difference in the rate of absorption.

TABLE 4.—Absorption of Digipuratum by Cats

Sex	Weight, Gm.	Mg. Leaf per Kg. Cat	Ether Started, Min.	Emesis, Min.	Died, Min.	Stomach	Oral Dose Absorbed, %
F.	2,720	300	47	0	149	Empty	13.7
M.	4,155	300	37	82	187	Empty	4
F.	3,270	300	33	98	151	Empty	5.6
F.	2,334	350	36	0	161	Empty	1
F.	3,025	300	30	90	152	Empty	1
M.	2,490	300	85	0	166	Empty	5.3

The results secured in the experiments with digalen are given in Table 5.

TABLE 5.—Absorption of Digalen by Cats

Sex	Weight, Gm.	Mg. Leaf per Kg. Cat	Ether Started, Min.	Emesis, Min.	Died, Min.	Stomach	Oral Dose Absorbed, %
F.	1,425	300	59	0	111	Empty	42.8
M.	1,725	300	62	55	135	Empty	35.6
F.	1,275	300	33	58	98	Empty	21.4

From these three experiments, it would seem that digalen is absorbed much more rapidly than either the tincture or digipuratum. That this means that digalen is to be preferred to the other preparation is by no means the case. While, as the average, the absorption of digalen in 114 minutes was about 33 per cent. of the dose administered, this in reality amounted to only about 8 per cent. of the tincture. So, at the end of the stated time, active principles had been absorbed from the digalen dose to amount to about 8 per cent. of the tincture, while, the tincture itself being given, the absorption amounted to 13 per cent.

It does not seem out of place to mention the relative cost of these preparations. We have recently had occasion to purchase a number of four ounce samples of physiologically tested tincture of digitalis from the local retailers, and the price was uniformly 40 cents, or at the rate of 10 cents an ounce. Digipuratum, in the form of tablets, retails in Richmond at 90 cents for twelve tablets, each tablet, according to our assays, being equivalent to a little less than 16 minims of a good tincture. Digipuratum, on this basis, equivalent to one ounce of a potent tincture, would cost about $2.25, or over twenty-five times as much as the tincture. With digalen the case is even worse. The half ounce containers of this preparation retail on the local market

for the same amount as the digipuratum package, that is, 90 cents. It has been shown, however, that digalen possesses only about one-fourth the physiological activity of the sample tincture. Since digalen retails at $1.80 an ounce, and since it requires four ounces of digalen to represent one ounce of the tincture, the cost of digalen in an amount equivalent to our four ounce sample would be about $28 instead of the 40 cents that the latter retails for.

The results obtained with digipoten are given in Table 6.

TABLE 6.—Absorption of Digipoten by Cats

Sex	Weight, Gm.	Mg. Leaf per Kg. Cat	Ether Started. Min.	Emesis, Min.	Died, Min.	Stomach	Oral Dose Absorbed. %
F.	2,180	300	49	0	109	Empty	16.3
F.	2,270	300	30	25	88	Full	33.2
F.	2,146	300	36	49	129	Full	0
F.	1,320	300	18	0	102	Empty	3.4
M.	3,305	300	25	40	65	Empty	13.9
F.	2,600	300	43	25	81	Empty	13.7

As the result of these six experiments, it seems that the absorption of digipoten is slightly more rapid than is the case with the tincture. After an average lapse of 95 minutes, an average absorption of about 13 per cent. of the administered dose occurred. It will be recalled that with the tincture the lapse of time was 112 minutes, with about the same amount of absorption.

When all the facts are taken into consideration, it is apparent that none of the special preparations have advantages over the official tincture from the point of view of absorption which would justify their employment to the exclusion of the former. While digalen is apparently absorbed more readily from the gastro-intestinal tract, the fact that this preparation is of very inferior strength, that different samples show decided variations in strength, and the enormous cost compared with that of a standardized tincture would outweigh the possible advantage of more rapid absorption.

The following conclusions may be drawn:

1. The official tincture of digitalis is absorbed more rapidly from the gastro-intestinal tract of cats than is the infusion made from the same leaf in the manner described.

2. The three special preparations of digitalis, namely, digipuratum, digalen, and digipoten, seem to possess no decided advantage over the official tincture. Digalen is absorbed more rapidly, but the variability in strength and the low standard of strength, together with the high cost of this preparation, more than offset this possible advantage.

VENTRICULAR ESCAPE WITH OBSERVATIONS ON CASES SHOWING A VENTRICULAR RATE GREATER THAN THAT OF THE AURICLES *

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The ventricles occasionally escape from the control of the sinu-auricular node through the independent action of their own center of stimulus production in the atrioventricular junctional tissues. Two types of such ventricular escape should be recognized: first, that which is dependent primarily on a depression of the pacemaker in the sinu-auricular node; and second, that which is dependent primarily on an excitation of the pacemaker in the atrioventricular node. As one would anticipate, examples of the first type are occasionally seen, while instances of the second type appear to be decidedly rare, though both conditions may be more common than we realize at present. The two factors, depression of the sinu-auricular node and the excitation of the atrioventricular node, may be found in a single case. The differentiation between the two types must be based largely on the rate of the sinu-auricular pacemaker from which the ventricles escape and upon the rate of the ventricular pacemaker which escapes. In the electrocardiogram the escaped ventricular complex is normal in shape, similar to that resulting from auricular excitation.

Sometimes the atrioventricular node may manufacture the stimulus for both auricles and ventricles, thus producing true atrioventricular rhythm. This should be distinguished from simple ventricular escape, for in atrioventricular rhythm only one pacemaker controls the heart, while in escape of the ventricles there are two pacemakers, both nodes functioning, the upper node for the auricles and the lower node for the ventricles. Atropin injected subcutaneously may release the lower node from vagal action before it releases the upper node, so that ventricular escape may occur temporarily, as pointed out by Gallavardin, Dufourt and Petzetakis;[1] or true atrioventricular rhythm may occur spontaneously after atropin for a few minutes, as pointed out in one case by Wilson[2] and as seen in a recent case at the Massachusetts General Hospital (Fig. 1). Wilson has produced this rhythm in a number of

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* From the Medical Service of the Massachusetts General Hospital.

1. Gallavardin, L.; Dufourt, P., and Petzetakis: Arch. d. mal du cœur, 1914, vii, 1.

2. Wilson, F. N.: The Archives Int. Med., 1915, xvi, 989.

subjects by the combined effect of early atropin action and ocular pressure or forced respiration. The differential diagnosis between ventricular escape and atrioventricular rhythm is very uncertain without the electrocardiogram. Errors may easily be made in the interpretation of polygrams, in the jugular records of which the *a* and *c* waves almost or completely coincide. Even if the shortened *a-c* or the *c-a* intervals are constant for a considerable stretch of record, ventricular escape may be occurring and not atrioventricular rhythm. In the electrocardiogram, however, we have in the shape of the auricular complex an invaluable clue to the true condition. If the shape of this complex is normal, we have evidence immediately that the sinu-auricular node is

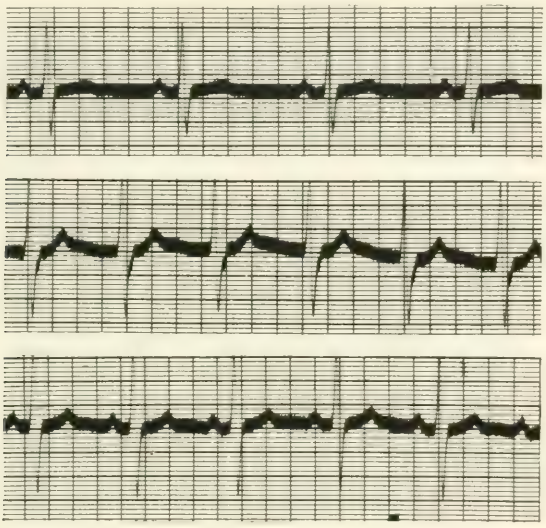

Fig. 1.—Lead 2 of electrocardiogram of E. B. Upper record, before atropin; middle record, fifteen minutes after atropin sulphate 0.002 gm. subcutaneously; and lower record, thirty minutes after the injection of atropin. In the upper and lower records normal rhythm arising in the sinu-auricular node is present; in the middle record occurs a transient atrioventricular rhythm, the inverted auricular complex falling at the end of the first ventricular complex. In all figures abscissae = 0.2 second, ordinates = 10^{-4} volts. The curves in this and the following illustrations are reduced to two-thirds size of the originals.

functioning; if the auricular complex is inverted (in Lead 2), and always at the same time interval immediately before or after the first ventricular complex, we may conclude that the atrioventricular node is probably controlling both auricles and ventricles.

The auriculoventricular dissociation found in ventricular escape is different from that found in complete heart block in that there is usually no defect in auriculoventricular conduction with it. In high-grade heart block, however, ventricular escape may occur as the result

of such a blocking of auricular stimuli that the idioventricular rhythm asserts itself, even though atrioventricular node and bundle may still be able to carry an impulse now and then.

TYPES OF VENTRICULAR ESCAPE

Belonging to the type of ventricular escape for which depression and slowing of the sinu-auricular pacemaker are primarily responsible, are several conditions. When the vagus nerve is overactive, forced expiration may produce a temporary dissociation of the auricles and ventricles, due to marked slowing in the rate of the auricle with resultant escape of the atrioventricular nodal pacemaker, as seen in

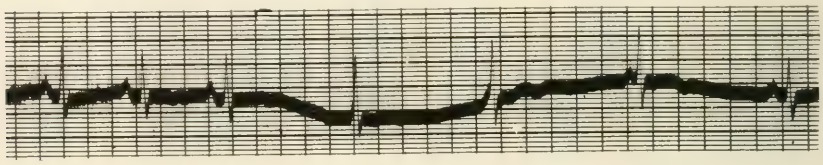

Fig. 2.—Lead 2 of electrocardiogram of G. A. M., showing ventricular escape as the result of forced expiration.

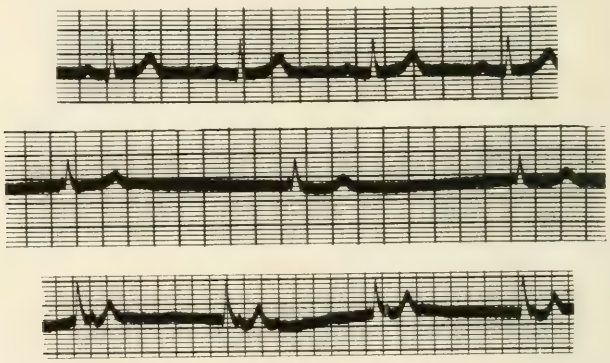

Fig. 3.—Lead 1 of electrocardiogram of G. H. A., showing auriculoventricular dissociation resulting from digitalis. In the upper record occurs the normal rhythm of the patient while not under the influence of digitalis.

Figure 2. Vagal pressure may also act to produce ventricular escape, by depressing the sinu-auricular nodal rate below that of the atrioventricular node (Fig. 6). Digitalis may be responsible for such a situation, as shown by Figure 3. Finally it may occur without obvious cause (Fig. 4). Gallavardin, Dufourt, and Petzetakis[1] have shown that the most varied figures of auriculoventricular superposition in polygrams and electrocardiograms may be produced by intermittent ventricular automatism, as in three patients with bradycardia who came under their observation.

An irritable atrioventricular node may show itself by ventricular escape, even when the rate of stimulus production in the sinu-auricular node is not low. In such cases the ventricular rate may be higher than the auricular rate. Recently at the Massachusetts General Hospital I have seen the ventricular rate spontaneously increased over that of the auricles in a woman 24 years of age who had suffered four weeks before from a peritonsillar abscess and who had had a tonsillectomy under ether four days before the cardiac peculiarity was discovered. She had had no drugs. After her tonsillectomy she had noticed slight but distinct palpitation, which she had never experienced before. Her rate was higher than usual, 90 to 100 instead of about 70. There was occasionally slight quickening of her pulse on palpation; until I obtained graphic records, I thought this slight arrhythmia might be due to auricular premature beats. An electrocardiogram showed auriculoventricular dissociation, with a ventricular rate of 96 and an auricular rate ranging from 67 to 85 (Fig. 5). The interventricular

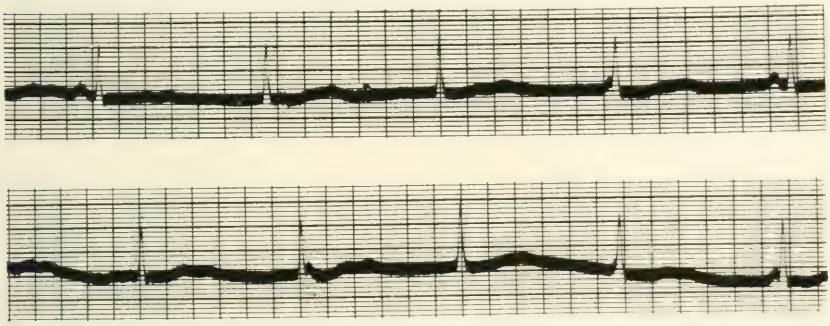

Fig. 4.—Lead 2 of electrocardiogram of A. P., showing auriculoventricular dissociation.

interval of 0.66 second was very constant, except when the auricular excitation came just after the ventricle had recovered from its refractory period and before enough time had elapsed for its escape. At such times the *P* deflection in the electrocardiogram is seen to fall on the *T* wave of the ventricular complex. A shortening of the interventricular interval *R* to *R* results, thus interrupting momentarily the ventricular dominant rhythm in the node of Tawara. In this patient interesting additional evidence was obtained as the result of her resumption of normal rhythm, at a rate of 78 to 83, the day after the dissociation was discovered, and the temporary return of the dissociation as the result of either right or left vagal pressure (Fig. 6). On this day the slowing of the pacemaker in the sinu-auricular node from 80 to 68 allowed the escape of the pacemaker in the atrioventricular node. Here apparently was an irritable atrioventricular node, less irritable on the

second day of examination than on the first, but still irritable enough to escape when the sinu-auricular rate was somewhat slowed. The immediate cause of this irritability appears to have been the tonsillectomy, but the modus operandi is a matter of conjecture at present. Aside from the dissociation in this case the heart appeared normal. The patient felt well and was up and about. Wilson[3] in 1915 reported a case in which, as the result of forced respiration, a dissociation of auricles and ventricles occurred with a ventricular rate of about 85 and an auricular rate of about 75. This was found in a man of 22 years.

An increase of the rate of the ventricles beyond that of the auricles is uncommon. Lea[4] in 1915 collected two cases from the literature and reported one himself in which the ventricular rate exceeded that of the auricles in complete heart block. Of these three cases, digitalis

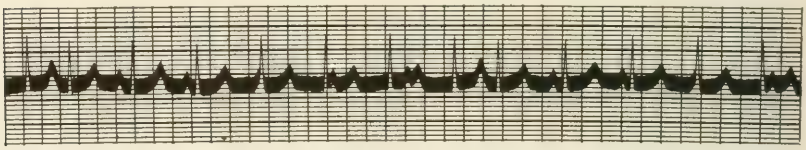

Fig. 5.—Lead 2 of electrocardiogram of J. R. O., showing spontaneous ventricular escape, with higher ventricular than auricular rate.

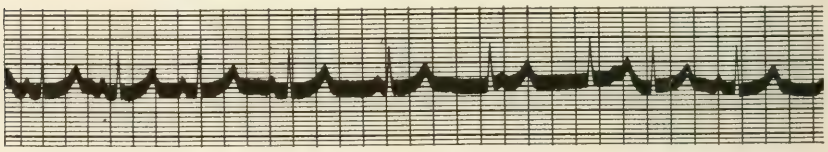

Fig. 6.—Lead 2 of electrocardiogram of J. R. O., showing transient ventricular escape resulting from pressure of left vagus nerve.

was apparently responsible for one (Meyer's) and strophanthus for another (Hewlett and Barringer's); Lea's patient had had no digitalis. A rate of the ventricles higher than that of the auricles occurred temporarily in a case of Gallavardin's[1] and in one of Wilson's[2] due to ventricular escape resulting from the administration of atropin. Forced respiration resulting in ventricular escape increased the rate of the ventricles over that of the auricles in the case of Wilson,[3] to which reference has already been made.

Three cases have come under my observation at the Massachusetts General Hospital which showed increase in the rate of the ventricles over that of the auricles. One, occurring spontaneously, has been described above; the other two can be directly ascribed to digitalis,

3. Wilson, F. N.: The Archives Int. Med., 1915, xvi, 86.
4. Lea, Edgar: Lancet, London, 1915, i, 1289.

in one the automatic ventricular rate varying from 65 to 82 while the auricular rate was constant at 41 to 43 (Fig. 7). In the first curve of Figure 7 a regular ventricular action of 82 to the minute occurred, every other beat apparently responding to a regular auricular action of 41 to the minute. In the lower record the shorter interventricular intervals which disturb the dominant rhythm of the ventricles are produced by transient auriculoventricular association, with prolonged *P-R* interval, as the result of the falling of the auricular deflection beyond the refractory period of the ventricle, but not late enough to allow the ventricular pacemaker to escape. In this case both factors in the production of ventricular escape are present. The other case in which digi-

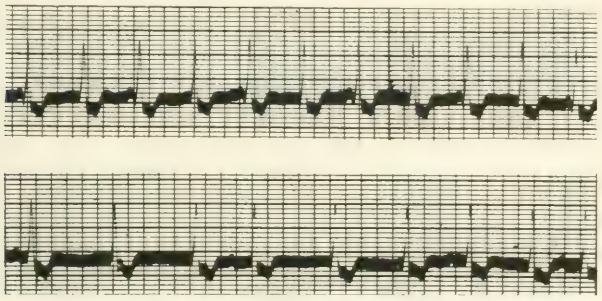

Fig. 7.—Lead 2 of electrocardiogram of E. J. Y., showing ventricular escape resulting from digitalis. In the upper record the ventricular rate is 82 and the auricular rate 41; in the lower record the ventricular rate is 65 and the auricular rate 43.

talis was responsible for the higher ventricular rate, was a patient with atrioventricular rhythm, in whom a curious bigeminy occurred after digitalis. This bigeminy consisted of the sandwiching of an auricular beat between two ventricular contractions; a full description of it may be found in a previous paper by the writer.

SUMMARY

Two types of ventricular escape are described: (1) the occasional type, in which the automatic stimulus production in the atrioventricular node is released by depression, and hence slowing, of the pacemaker in the sinu-auricular node; and (2) the rare type, in which the atrioventricular nodal center of stimulus production is so irritable that it escapes from the control of the sinu-auricular node. Both factors, depression of the upper node and irritation of the lower node, may play a part in ventricular escape in a single case, as in an instance reported, in the production of which digitalis apparently was the important factor. Three cases are recorded in which the ventricular rate exceeded that of the auricles.

5. White, P. D.: The Archives Int. Med., 1915, xvi, 517.

A STUDY OF PROTEINS IN URINE

AND A COMPARISON OF GRAVIMETRIC AND NEPHELOMETRIC METHODS FOR THEIR ESTIMATION *

J. T. W. MARSHALL, H. W. BANKS, 3d
AND
S. S. GRAVES

Analytic methods depending on the optical properties of a finely divided suspension have recently achieved considerable prominence. Both the turbidimeter and the nephelometer have been used successfully in quantitative work when the amounts of material were too small to weigh or when the recovery of the substance to be weighed demanded long and tedious manipulation. The quantitative determination of albumin in urine presents many of these difficulties. This fact was pointed out by Folin and Denis[1] in a paper published in 1914, in which a method was described whereby a quantitative estimation of protein in urine could be performed rapidly by means of the turbidimeter. The results obtained agreed well with gravimetric determinations. Since a method depending on the amount of light reflected by a turbid liquid should permit of the determination of smaller quantities of material than one in which the absorbed light is measured, it was thought that the application of the nephelometer to this problem might be of value. While the accuracy of the method proved no greater than that reported by Folin and Denis, some interesting results were obtained and are here presented. Also, since a nephelometer involving slightly new principles had been devised by two of us, it was thought that this problem would afford an opportunity for the systematic comparison of this new instrument with one of the plunger type previously used by Kober and Graves.[2]

The Marshall and Banks nephelometer used in the preliminary work was built on the frame of a Duboscq colorimeter, but differs in two fundamental respects from the plunger instrument. Instead of a variable length of illuminated column, the suspensions are contained in cells of equal height, somewhat resembling small polariscope tubes. The beam of light is normal to the axes of these cells, as in other nephelometers, and photometric balance is effected by means of a movable wedge of neutral-tinted glass placed above one of the cells. The

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* From the Harriman Research Laboratory, the Roosevelt Hospital, New York.

1. Folin and Denis: Jour. Biol. Chem., 1914, xviii, 273.
2. Kober and Graves: Jour. Am. Chem. Soc., 1914, xxxvi, 1304.

position of the movable wedge is read from a suitable scale with vernier. In making observation photometric balance is first obtained with identical suspensions in both tubes. The wedge reading gives what may be termed the zero point If now unequal suspensions are compared (the stronger one being placed under the wedge), the illumination of the field will be unequal. By moving the wedge so that the light from the cell below must traverse a greater thickness of absorbing medium, photometric balance is restored. From a calibration of the wedge and the difference between the zero point reading and the new reading, the relative intensities of the lights reflected by the two suspensions may be calculated, as in the case of other wedge photometers. This instrument, therefore, possesses the advantage that the actual ratios of lights reflected from different suspensions may be determined, a very important requirement for the theoretical consideration of the problem of nephelometry in general. The application of this principle to the calculation of results will be referred to later. The determination of the zero reading with each series of observations largely eliminates errors arising from stray light and changes in illumination.

In the first experiments on the estimation of urine protein by means of this instrument the standard (human blood serum) and precipitant (sulphosalicylic acid) recommended by Folin and Denis were used. The results were compared with gravimetric determinations made according to Scherer's method. In determinations on daily specimens of urine from one patient the nephelometric results were consistently about 25 per cent. higher than the gravimetric, while in the case of another individual the nephelometric results showed wide variations from the gravimetric, being usually much higher. This suggested that there was a difference in the nature of the protein excreted by these two individuals. The most probable explanation of such a difference would seem to be that albumin and globulin, while closely related chemically, might give, when precipitated from solutions of equal concentration by sulphosalicylic acid, very different amounts of light, and that in the two cases mentioned the proportion of albumin to globulin was not the same. Since the protein excreted in the urine is at least closely allied to the proteins of the serum, albumin, euglobulin and pseudoglobulin were prepared from horse serum. Solutions of these three proteins were made and standardized by Scherer's method. These solutions were then diluted so that their protein content was the same, precipitated with sulphosalicylic acid and compared in the nephelometer with a standard casein suspension.[3]

3. This was used as the standard of reference in such comparative work because of the ease with which solutions of known strength may be prepared; furthermore, the precipitation of such solutions with sulphosalicylic acid gives a cloud of great permanence.

It was found that under the above conditions albumin gave about twice as much light as euglobulin and about two and a half times as much light as pseudoglobulin. Mixtures of these protein solutions gave, in general, less light than the constituents singly. It is no doubt safe to assume that the proteins excreted in the urine would behave in a similar manner; and as no definite value for the ratio of albumin to globulin can be assumed in dealing with various specimens of urine, quantitative estimations of total protein should not be made with a precipitant which gives unequal clouds with the different proteins. It is thus evident that sulphosalicylic acid is not satisfactory for the nephelometric determination of protein in urine. Two possible methods of overcoming this difficulty suggested themselves: either to determine the protein fractions separately by accentuating these differences, or to attempt to find a precipitant which would give essentially the same cloud with a definite amount of mixed proteins, no matter how the proportions of albumin and globulin varied. The latter course was decided on. Many of the reagents commonly used for the precipitation of proteins were at once eliminated owing to their evident unfitness for nephelometric work. For instance, any method of precipitation which depends on "salting out" reactions presents many difficulties owing to the high salt content of the solutions used. Again, salts of the heavy metals seem to favor rapid agglutination of the suspension. Trichloracetic acid fulfilled most of the requirements for a suitable precipitant, but it had to some extent the defect of sulphosalicylic acid; also the amount of cloud varied with the time. Metaphosphoric acid gave practically the same amount of cloud with each of the three protein solutions. A 1 per cent. solution was found to be sufficient for precipitation. An increase in the concentration of the acid up to 5 per cent. had no appreciable effect on the cloud produced. The precipitates, however, agglutinated too rapidly to permit of nephelometric comparison. Of a number of protective colloids tried, gum arabic solution proved the most satisfactory with this reagent and prevented the agglutination of the suspension up to half an hour.

As metaphosphoric acid is never entirely free from the ortho-acid, and as the amount of the latter constantly increases in a solution of the former, it seemed necessary to determine what effect the presence of orthophosphoric acid had on the precipitation.[4] The following table shows the effect of varying proportions of the two acids in the precipitation of 0.04 per cent. mixed protein solution with gum arabic as a protective colloid.

4. The metaphosphoric acid used was the common glacial stick acid. This contains considerable amounts of ortho-acid and sodium phosphate for which no allowance is made in the above figures. The ortho-acid was syrupy H_3PO_4, 84 per cent.

TABLE 1.—Plunger Instrument: Standard 0.005 Per Cent. Casein Solution + Sulphosalicylic Acid; Set at 20 Mm.

Concentration of Acids, per cent.	Meta.	1.0	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.0
	Ortho.	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Reading, Mm.		23.6	22.7	22.7	22.5	22.7	22.6	22.0	21.9	21.9	22.0	No cloud

With the mixture 0.4 per cent. metaphosphoric acid and 0.6 per cent. ortho-acid the slight decrease in the reading indicates a slight increase in the cloud. An increase in the proportion of the ortho-acid produces no further change up to and including the ratio of 1 to 9. Thus the precipitation appears to be more complete with a solution containing an excess of orthophosphoric acid. As the amount of this acid has no effect between the limits indicated, it was decided to use as the precipitant a mixture containing 0.6 per cent. and 0.4 per cent. of the ortho-acid and meta-acid respectively. A large amount of the meta-acid may thus be hydrated before a noticeable change occurs in the cloud.[5]

TABLE 2.—Plunger Instrument: Standard 0.005 Per Cent. Casein + Sulphosalicylic Acid; Set at 20 Mm.

Relative Amounts of 0.04 per Cent. Protein Solution			Readings, Mm.		
Albumin	Euglobulin	Pseudo-globulin	5 Min.	10 Min.	15 Min.
10	0	0	21.7	21.6	21.5
0	10	0	21	20.9	21.1
0	0	10	21.5	21.5	21.5
6	2	2	21.5	21.5	21.6
8	1	1	21.6	21.5	21.6
5	2.5	2.5	21.2	21	21.1
4	3	3	21	21.2	20.9

It was then necessary to determine what variations there were in the clouds produced when the three proteins separately and mixed were precipitated by this reagent in the presence of gum arabic. The comparisons were made as before against a standard casein solution precipitated by sulphosalicylic acid. Five c.c. of 0.04 per cent. protein

5. Experiments in duplicating the hydrogen ion concentration of this mixture by adding hydrochloric acid to solutions of metaphosphoric were inconclusive, due possibly to the difficulty of employing indicators with phosphoric acids. Thus we cannot at present say whether the change in hydrogen ion concentration is alone responsible for the effect. At all events, the mixture of the two phosphoric acids appeared to be the most satisfactory reagent.

solution were used in each case; to this were added 5 c.c. of 1 per cent. gum arabic solution, and, after thorough mixing, 20 c.c. of the reagent run in from a pipette. Readings were made at intervals of five, ten and fifteen minutes after precipitation. Agglutination did not occur for more than thirty minutes.

From these results it is evident that there are no appreciable differences between the proteins themselves or various mixtures of them as regards the clouds produced under these conditions.

The next consideration was to determine upon a satisfactory standard. Nephelometric results may be interpreted quantitatively in one of two ways: either the substance to be determined may be compared to a solution of known strength of the same substance, or it may be compared to a purely arbitrary standard. In the present problem the former of these methods was not entirely practicable, owing to the difficulty of preparing pure urine proteins. Again, in dealing with these proteins the solutions cannot be made up to a given strength by weighing out the dried substance and dissolving in a known volume of water; the solution must be standardized by some other method. Since, then, the identical substance cannot be used as a standard, an attempt was made to realize the conditions of the first method as closely as possible. The assumption was made that since the various serum proteins showed no differences with this precipitant, the closely related urine proteins should give the same amount of cloud. Thus, if two solutions, one of urine protein, the other of serum protein, give in the instrument identical clouds, we may assume that they contain equal amounts of protein. An aqueous solution of serum proteins may be standardized with reasonable accuracy by nitrogen estimation[6] or by gravimetric determination of the heat coagulable protein. In the case of protein in urine such a standardization obviously presents many difficulties, owing to adsorption of other ordinary constituents. Serum protein, however, is not a convenient standard for practical work, for when the serum is not perfectly fresh, the suspensions agglutinate rapidly.

Other proteins were then investigated. It was found that solutions made from commercial dried egg-albumin and standardized gravimetrically gave the same cloud in the instrument as serum protein solutions of the same strength similarly standardized. It is thus evident that such a solution may be substituted for the serum protein solution as a standard. This is desirable in that egg-albumin is easily obtained and solutions are readily prepared and standardized. The standard solution of this substance was prepared as follows: About 5 gm. of

6. Allowance for nonprotein nitrogen must be made and in the gravimetric determinations precautions described later must be observed.

commercial dried egg-albumin were dissolved in 450 c.c. of water, with the addition of 2 gm. of powdered talc. After agitation 50 c.c. of 2 per cent. tricresol were then added and the mixture filtered through a fluted paper. This gave a nearly clear solution containing about 9 mg. of heat-coagulable protein per cubic centimeter. Furthermore, egg-albumin solutions prepared as described above are very stable and thus large quantities may be made up at one time. For example, a solution containing at the time of preparation 9.2 mg. of coagulable protein per cubic centimeter contained after forty days 9 mg. per cubic centimeter.

TABLE 3

Protein	Amount and Dilution, C.c.	Mg. Protein Recovered	Mg. Nitrogen in Protein	Per Cent. Nitrogen in Protein	Mg. Nitrogen in Filtrate
Egg-Albumin, Solution 1, 10 c.c. = 7.89 Mg. N.	5 + 95 water	23.5	3.52	14.98	0.54
	10 + 90 water	46.3	7.02	15.17	1.05
	20 + 80 water	92.1	13.88	15.08	1.95
Egg-Albumin. Solution 2, 10 c.c. = 15.96 Mg. N.	10 + 490 water	91.9	13.63	14.84	1.90
	10 + 150 water	92.4	13.94	15.10	1.84
	10 + 120 water + 20 normal urine	90.5	13.84	15.28	....
	10 + 100 water + 40 normal urine	92.4	13.98	15.11	....
	10 + 90 water boiled 1 hour	93.0	14.04	15.10	1.75
	10 + 90 water excess acetic acid	92.8	14.11	15.20	1.85
Serum-Albumin Solution, 10 c.c. = 12.36 Mg. N.	5 + 95 water	79.3	11.74	14.80	....
	10 + 90 water	158.8	23.26	14.80	1.28
	20 + 80 water	319.5	46.30	14.79	2.60
	5 + 95 normal urine	79.4	.....	.....	....
	10 + 90 normal urine	157.4	.....	.....	....

As previous work had given evidence that it was difficult to obtain reproducible results by Scherer's gravimetric method, a study of some of the factors involved in the coagulation, filtration and drying of egg-albumin, serum protein and urine protein was undertaken. This was necessary, as a consistent standard of comparison was essential to the interpretation of the nephelometric results. Solutions of the proteins mentioned were coagulated by heat with the cautious addition of 1 per cent. acetic acid. The coagulated protein was then filtered on weighed Gooch crucibles,[7] washed with hot water, finally with alcohol, and dried

7. These were used to eliminate the uncertainties arising from the use of the weighed filter papers usually recommended.

at from 100 to 105 C. to constant weight. In a number of cases drying was found to require as much as two days; after this there was no further loss of weight. The crucibles were cooled over phosphorus pentoxid for one hour before weighing. The filtrates, although clear, were always tested with sulphosalicylic acid for uncoagulated protein.

Aqueous solutions of egg-albumin were first studied. The total nitrogen content of the solution was determined by the Kjeldahl method; portions were then coagulated and filtered as described above. Kjeldahl determinations were also made on the filtrates and on the coagulated protein in the crucibles.[8] The nitrogen determinations on the coagulated protein agreed with the figures recorded by other investigators only when the foregoing precautions in drying were observed.

Changes in the dilution, in the amount of protein present, in the amount of acid, and in the time of heating were studied. In some cases normal urine was added as shown in Table 3, where the results are recorded.

The results show that when the precipitates are dried to constant weight, the conditions of precipitation may vary considerably and still permit of reproducible results in the amount of protein recovered. Even in the presence of normal urine there is apparently no error due to adsorption.[9]

The nitrogen content of the coagula agrees well with the figure found (15.21 per cent.) for larger quantities of egg-albumin coagulated and dried to constant weight, and is in good agreement with the accepted value. The sum of the protein nitrogen and the nitrogen of the filtrate approximates very closely the nitrogen of the solution. As is shown (column 5, Table 3), the nitrogen of the filtrates is directly proportional to the amount of protein coagulated. Nonprotein nitrogen determined by the Greenwald method[10] gave about 0.1 mg. in 10 c.c. of solution. Further experiments showed that the high nitrogen of the filtrates from the coagula was due to ovomucoid contained in egg-albumin. This substance is not precipitated by trichloracetic acid, but is removed by the kaolin used in the Greenwald method.

The coagulation of the protein in pathologic urine was then studied in the same manner, except that for obvious reasons the nitrogen of the filtrate was not determined. By following the method here outlined the results checked very closely where duplicate determinations

8. Any protein which adhered to the beaker was digested in the beaker with 1 c.c. sulphuric acid and the nitrogen determined. The amounts found were in most cases negligible.

9. The high color of protein coagulated from pathologic specimens containing albumin would, however, indicate considerable adsorption.

10. Greenwald: Estimation of Nonprotein Nitrogen in Blood, Jour. Biol. Chem., 1915, xxi, 61.

were made, and the errors due to solution, adsorption, etc., were at least constant for a given specimen of urine, although it is highly probable that the absolute amount of protein present was not obtained. The nitrogen in the coagulated urine protein was always lower than expected.

The study of the nephelometric determination was then undertaken. Since the light observed in the instrument is not proportional to the amount of material, the relationship between concentration and instrumental readings must be determined for the substance and the precipitant. This may be done by observing in the instrument suspensions prepared from solutions of known relative concentrations, irrespective of their absolute concentrations.[11] The solutions for comparison were prepared as follows: A urine containing albumin was suitably diluted for use as a stock solution. A series of solutions was then prepared from this by taking quantities of 9 c.c., 8 c.c., 7 c.c., 6 c.c. and 5 c.c. and making each up to a volume of 10 c.c. with distilled water. These were then precipitated and compared in the instruments with the stock solution similarly precipitated. From the readings thus obtained a curve was drawn by plotting the ratio of concentration against the readings of the instruments. These curves may now be used in the determination of protein solutions of unknown concentration, by means of a suitable standard. Either the ratio may be read directly from the curve, or it may be calculated from the equation of the curve. The latter method was used throughout this investigation. In the plunger instrument the following formula[12] was used:

$$y = \frac{s}{x} - \left\{ \frac{1 - x}{x^2} \right\} sk$$

The value of k in this case was found to be 0.20. In the wedge instrument the somewhat similar curve is also capable of formulative interpretation. It was found that by plotting the wedge readings less the zero point reading against the logarithm of the ratio, a straight line resulted. The ratio may thus be expressed by the following formula:

$$\left\{ \log. \frac{1}{R} = KW \right\}$$

In this formula W is the wedge reading less the zero reading, R is the ratio of the weaker solution to the stronger; K, a constant depending on the substance and the precipitant used, is determined from the

11. A precaution to be exercised is that the solutions must not be too dilute to be read conveniently, or so strong that they agglutinate rapidly.

12. Jour Biol. Chem., 1913, xiii, 491.

observations on known ratios referred to above.[13] The evaluation of K from known ratios of urine protein is given in Table 4. When the ratio to the standard has been obtained, the calculation of the amount of protein simply depends on the protein content of the standard and the dilution of the unknown urine. It is advisable to dilute the urine so that the ratio to the standard is fairly close to unity.

TABLE 4.—Evaluation of Constant K *

W	7.8	16.0	26.6	41.0	54.4
R	0.9	0.8	0.7	0.6	0.5
K × 10^3	5.9	6.0	5.8	5.4	5.5

* The weighted mean, K = 5.7 × 10^3, was used.

The method of precipitation used throughout this investigation was as follows: Five cubic centimeters of standard egg-albumin solution containing about 0.5 mg. protein per cubic centimeter and 5 c.c. of previously diluted urine were measured into dry Erlenmeyer flasks. To each flask was then added 5 c.c. of 1 per cent. gum arabic solution, and finally 20 c.c. of the phosphoric acid reagent. The suspensions were then compared in the nephelometer and the calculations performed as has been indicated. The gum arabic solution should be prepared fresh each day, but this presents little difficulty, as extreme accuracy is not necessary. The stability of the standard has already been referred to. The precipitant (0.6 per cent. orthophosphoric, 0.4 per cent. metaphosphoric) was prepared each day from 5 per cent. solutions of the two acids. It was found that the 5 per cent. solution of metaphosphoric acid after standing ten days was still satisfactory for the preparation of the reagent, for even though much of the acid may have been hydrated in this time, if the proportion of orthophosphoric did not exceed 90 per cent. of the total acid, the precipitating power of the mixture apparently was not altered.

In the case of urines highly colored with bile pigments, blood, etc., color may interfere with the determination. With such specimens the difficulty may be overcome by the following procedure: Two equal portions of the urine are taken, to one of which is added a known amount of the standard egg-albumin solution, and each then made up to an equal volume with water and compared in the usual manner. The original protein content of the urine may thus be obtained indirectly,

13. Since the light is an expotential function of W it can easily be shown that the light reflected by a suspension is equal to $C^{K/k}$ where C is the concentration of the suspension and k is a constant depending on the particular wedge used. K has been referred to previously.

and difficulties arising from differences of color are entirely obviated. It was not necessary to use this method in any of the determinations listed below, but experience has shown that it is eminently practicable, though somewhat less accurate than the direct method.

Nephelometric determinations were made on daily specimens of urine from several nephritics during a period of several weeks. The protein content of each specimen was also determined gravimetrically in the following manner: The protein was coagulated by heat and dilute acetic acid, filtered on weighed Gooch crucibles, washed with hot water and alcohol and dried in the air oven at 100 to 105 C. for two days. The filtrates were tested with sulphosalicylic acid for uncoagulated protein. The nitrogen content of the protein recovered was in each case determined by the Kjeldahl method.

Although the inaccuracies of the Esbach determination are well known, it is so much used in clinical practice that it was thought advisable to make such determinations on a number of specimens in this series. These determinations were made in the usual manner and were read after standing twenty-four hours. All these results are included in Table 5, which presents a summary of work on urine.

It may also be seen from column 1 (Table 5) that the actual amount of protein recovered was seldom less than 60 mg. We have found that satisfactory duplicate determinations can readily be made on amounts of protein of about this order. Column 2, the percentage of nitrogen in the protein recovered, is remarkably consistent in the cases of W. and M. In the other two cases studied we find decidedly greater variations. The average of W. and M. (14.3 per cent.) is much lower than would be expected for protein of this kind. The factor, 6.3, recommended in the literature for calculation of urine protein content from the nitrogen content of the coagulum, corresponds to a nitrogen percentage of 15.88. This is very much above the average nitrogen value even in cases Mc. and C. (14.6 per cent. and 15 per cent., respectively). This would indicate that occlusion of substances low in nitrogen was considerable and that the weight of the dry coagulum was not the weight of protein present in the sample of urine taken for analysis. This may be partially compensated for by the fact that it is not possible to obtain absolutely complete coagulation of the protein. The filtrates, however, never showed more than a slight trace of protein on the addition of sulphosalicylic acid and were generally protein free by this test. The error from this cause is therefore small. Columns 3, 4 and 5 are self-explanatory.

Columns 6 and 7 give the ratio of the determinations by the two nephelometers to those by the gravimetric method. In the case of W. the nephelometric determinations are, on the average, lower than the gravimetric. With M. the difference is less, but still in the same sense.

TABLE 5.—Protein Determination Obtained by Various Methods

Subject	Date	1 Gravimetric, Mg. Weighed	2 Kjeldahl, per Cent. N	3 Gravimetric, Mg. per C.c.	4 Plunger Neph., Mg. per C.c.	5 Wedge Neph., Mg. per C.c.	6 Col. 4 / Col. 3	7 Col. 5 / Col. 3	8 Esbach, Mg. per C.c.
W.	Feb. 2	157.3	.....	15.7	13.9	14.9	0.884	0.947	....
	3	164.9	14.53	16.5	13.0	15.6	0.788	0.946	....
	4	195.2	14.24	19.5	18.4	17.7	0.943	0.907	....
	5	72.9	14.32	14.6	....	13.9	.....	0.953	....
	14	66.0	14.27	13.2	11.6	....	0.878	.....	11.6
	17	76.1	.....	15.2	13.0	14.0	0.854	0.923	10.8
	18	54.0	14.26	10.8	10.2	....	0.944	.....	....
	20	59.0	14.10	11.8	11.5	11.5	0.975	0.978	5.8
	24	179.1	14.24	17.9	....	19.0	.....	1.061	8.6
	25	80.2	14.69	16.0	14.6	16.5	0.910	1.028	12.0
	26	93.9	14.35	18.8	17.5	18.7	0.932	0.996	12.4
Average			14.34	....	....	....	0.901	0.971	
Probable error	Mean		±0.03	....	....	....	±0.013	±0.011	
	Single determination		±0.11	....	....	....	±0.038	±0.033	
M.	Feb. 4	32.6	14.42	3.26	....	3.04	.....	0.932	....
	5	76.4	.....	3.06	3.00	2.99	0.982	0.978	....
	15	102.6	14.29	2.05	2.05	....	1.001	.....	1.3
	16	84.5	14.38	3.38	3.12	....	0.932	.....	2.3
	17	71.7	14.61	2.86	2.68	2.94	0.927	1.025	1.8
	18	69.6	14.18	2.78	2.69	....	0.967	.....	....
	19	76.6	.....	3.06	2.95	3.02	0.963	0.987	1.7
	20	62.2	14.29	2.49	2.51	2.51	1.009	1.009	1.4
	24	129.8	13.84	5.19	4.97	5.38	0.957	1.036	2.7
	25	130.7	14.38	5.23	5.24	....	1.002	.....	4.3
	26	96.3	14.68	3.85	4.06	3.75	1.054	0.973	3.6
Average			14.30	....	....	....	0.978	0.991	
Probable error	Mean		±0.05	....	....	....	±0.018	±0.008	
	Single determination		±0.15	....	....	....	±0.057	±0.021	
Mc.	Feb. 18	38.4	.....	1.54	1.94	....	1.262	.....	....
	20	54.3	13.87	1.09	1.27	1.25	1.170	1.152	0.5
	23	36.1	.....	0.72	0.94	1.00	1.303	1.365	....
	24	28.9	14.78	0.58	0.90	0.91	1.537	1.583	0.5
	25	66.7	15.14	1.33	1.64	1.62	1.229	1.213	1.2
	26	83.6	14.56	3.34	3.50	3.94	1.047	1.178	3.3
Average			14.60	....	....	....	1.261	1.302	
Probable error	Mean		±0.14	....	....	....	±0.047	±0.055	
	Single determination		±0.31	....	....	....	±0.115	±0.123	
C.	Feb. 2	99.4	14.38	3.98	4.17	3.87	1.048	0.973	....
	3	82.8	15.06	3.31	3.75	3.33	1.132	1.006	....
	4	102.9	15.75	4.12	....	4.17	.....	1.012	....
	5	90.1	14.62	3.60	3.66	3.57	0.991	0.991	....
Average			14.98	....	....	....	1.060	0.995	
Probable error	Mean		±0.20	....	....	....	±0.026	±0.006	
	Single determination		±0.40	....	....	....	±0.045	±0.012	

With Mc., however, the average is nearly 30 per cent. higher than the gravimetric determination. Again, with C. the ratio is very nearly unity. As for the explanation of these irregularities, it may be said in the first place that the gravimetric determination cannot be taken as the value of the absolute amount of protein present. Calculation of the results on the basis of the nitrogen content of the coagulated protein did not improve agreement—in fact the probable error of these determinations was greater than when the nephelometric determinations were referred to the gravimetric. This would indicate that while there may be errors in the gravimetric method, due to occlusion and other causes, the main source of the error lies in the nephelometric determinations themselves. These irregularities are probably due to differences in the form of the precipitants under different conditions. As the urines must be diluted according to their protein content, the amounts of the other urinary constituents will vary considerably. The effect of varying salt concentration on the state of a finely divided suspension is well known. The very large variations in the case of Mc. can hardly be accounted for in this way. The nitrogen value of the coagulated protein was not constant in successive specimens. The presence of a variable amount of mucoid might have some influence on the precipitation of albumin in the nephelometer. This is not precipitated by an excess of metaphosphoric acid, but it may act as a protective colloid and thus influence the state of protein precipitation. Removal of patient Mc from the hospital prevented a further study of this interesting irregularity.

From column 8 it may be seen that the Esbach determination did not agree with the nephelometric or the gravimetric, in the majority of cases being from 25 to 50 per cent. lower.

The probable errors show slightly more consistent results with the wedge instrument.

We may safely conclude that the nephelometric method is satisfactory for clinical purposes; and that the results are in fair agreement with those obtained by the gravimetric method. For urines of low protein concentration the method is no doubt more accurate than the gravimetric. It is much more rapid than the gravimetric or the Esbach determinations.

SUMMARY

1. A nephelometric method, using egg-albumin as a standard, for the determination of protein in urine has been described.

2. A new type of instrument has been used and a formulative expression for the relation between light and concentration has been given.

3. The factors involved in the quantitative recovery of protein from urine have been studied.

4. The nitrogen content of the protein recovered has been found to be lower than the generally accepted values in the case of urine protein.

5. Results with the wedge and with the plunger instruments have been compared with a gravimetric method.

The authors wish to express their thanks to Mr. Herbert Eckweiler for his careful work in the nitrogen determinations.

TRANSIENT AURICULAR FIBRILLATION

AN ELECTROCARDIOGRAPHIC STUDY *

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In this communication are presented the results of a detailed study, by means of the electrocardiograph, of six individuals exhibiting the change from a normal heart rhythm to that of auricular fibrillation. Although the disturbance of cardiac mechanism that causes this type of cardiac irregularity—incoordinate contraction or fibrillation of the auricular musculature—has been understood only during the past few years, its clinical prototype, the pulsus irregularis perpetuus of Hering, or the totally irregular pulse, has for years been recognized as one of the commonest as well as one of the gravest forms of cardiac arrhythmia. Perhaps from the widespread use of Hering's terminology, however, the erroneous impression has been prevalent that this condition once present is practically always permanent. Already a sufficient number of cases have been published to combat this view, so that we must now consider that auricular fibrillation, like the other disturbances of the cardiac mechanism—premature contractions, heart block and alternation—may, though less frequently, occur in a transitory as well as a permanent form. My main thesis will be to show not only that transient auricular fibrillation constitutes a well recognized condition, but that it may be subdivided into three well-defined groups.

REVIEW OF THE LITERATURE

Cushny and Edmunds,[1] in the paper that first propounded the theory that a totally irregular pulse is due to fibrillation of the auricles, were led to their experimental work by the study of a woman who had had numerous paroxysmal attacks of fibrillation during several years of observation. No determining factor was discovered clinically, but the conclusion was reached that the attacks were due to reflex vagus inhibition.

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* From the John Herr Musser Department of Research Medicine, University of Pennsylvania, Philadelphia.

1. Cushny, A. R., and Edmunds, C. W.: Paroxysmal Irregularity of the Heart and Auricular Fibrillation, Am. Jour. Med. Sc., 1907, cxxxiii, 66.

Very similar cases have been reported by Fox,[2] Hornung,[3] G. C. Robinson,[4] Popper,[5] and Lewis and Schleiter.[6] These patients, as was Cushny and Edmund's patient, were all over 50 years of age and had had numerous attacks, lasting from a few minutes or hours to several days, and extending over many years. In none was a valvular defect present, but hypertension and preponderance of the left ventricles were found in all. Another interesting group of ten cases has been reported by Heitz,[7] together with polygraphic records, which unfortunately do not absolutely preclude the existence of some other form of arrhythmia. In another series, out of a total of 120 patients with auricular fibrillation examined electrocardiographically, Fahrenkamp[8] found only four in whom the trouble was transient (3.3 per cent.). Though paroxysmal in character, the attacks were all single and short (one fatal), seen in acute conditions, such as Graves' disease, pneumonia and septicemia. Further details of these cases will be considered later, in connection with the discussion of the cases here reported. The cases reported by Falconer and Dean[9] and by Schwarzmann[10] developed transient attacks of fibrillation in the presence of an already existing heart block. The complication that this causes makes it inadvisable to include them in this discussion.

The older theory that a temporarily but totally irregular pulse (delirium cordis) is not uncommon and frequently disappears under digitalis medication was in most cases due to imperfect observation. The probability is that in such cases the slight degree of arrhythmia, which became still less with the improvement of the patient, became unnoticeable to the touch, in spite of the fact that the underlying condition of fibrillation persisted. In some cases, also, as Fahrenkamp and others have pointed out, the occurrence of complicated groups of extrasystoles may (in the absence of electrocardiograms) present a picture indistinguishable from auricular fibrillation.

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2. Fox, G. H.: Transitory Delirium Cordis, Am. Jour. Med. Sc., 1910, cxl, 815.
3. Hornung, O.: Ueber atypische tachykardische Paroxysmen, Deutsch. Arch. f. klin. Med., 1907, ??, 469.
4. Robinson, G. C.: Paroxysmal Auricular Fibrillation, The Archives Int. Med., 1914, xiii, 298.
5. Popper, H.: Ueber Anfälle von Vorhofflimmern, Med. Klin., 1915, xi, 885.
6. Lewis, T., and Schleiter, H. G.: The Relation of Regular Tachycardias of Auricular Origin to Auricular Fibrillation, Heart, 1911-1912, iii, 173.
7. Heitz, J.: La forme paroxystique de l'arythmie complete, Ann. de méd., 1914, i, 483.
8. Fahrenkamp, K.: Vorübergehende komplette Herzunregelmässigkeiten unter dem klinischen Bilde der Arythmia Perpetua mit Beobachtungen über Vaguswirkung, Deutsch. Arch. f. klin. Med., 1914, cxvii, 1.
9. Falconer, A. W., and Dean, G.: Observations on a Case of Heart Block Associated with Intermittent Attacks of Auricular Fibrillation, Heart, 1911-1912, iii, 247.
10. Schwarzmann, G. S.: Ueber ein Fall von Herz Block mit Paroxysmalem Vorhofflimmern, Zentralbl. f. inn. Med., 1914, xxxv, 1001.

The six cases of fibrillation mentioned above are here reported in detail, in the hope that they may throw some light on the poorly understood pathogenesis of this common and serious condition and on the prognosis of such transient cases. The fibrillation in four of the cases was found to be transient, and in the other two cases developed while the patients were under observation. These four represent 7.5 per cent. of the total number of cases of auricular fibrillation studied electrocardiographically at the University Hospital during a period of two

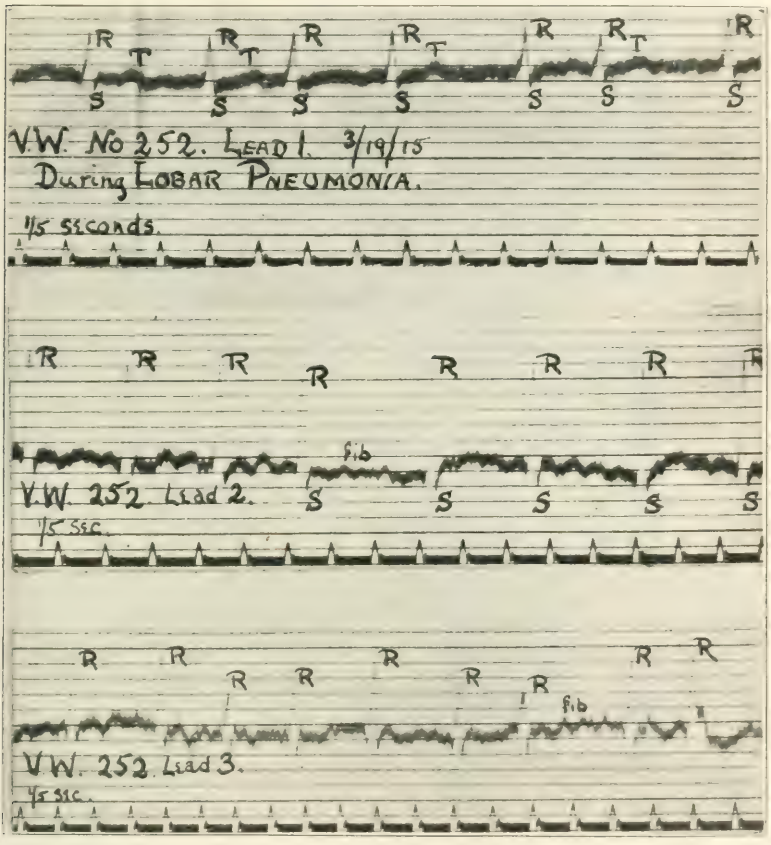

Fig. 1 (Case 1).—Electrocardiogram of V. W., showing transient auricular fibrillation in lobar pneumonia. In this, as in other electrocardiograms of this series, records were taken from the three customary leads. The tension of the string was so standardized that 1 millivolt caused a deflection of 1 cm. As the string could not be standardized with the patient in circuit, 1,400 ohms were added as an arbitrary equivalent of the patient's resistance. Platinum string, resistance about 3,500 ohms. Time intervals are expressed in fifths of second and occasionally by vertical lines indicating $\frac{1}{5}$ and $\frac{1}{25}$ second. In this figure, note (1) absence of sign of auricular contraction (P wave); (2) ventricular arrhythmia (irregular occurrence of R); and (3) occasional coarse waves of fibrillation.

and a half years. While this is apparently an unusually high percentage of transient fibrillation, it is very probable that the wider use of graphic methods of registration will in the near future demonstrate its greater frequency.

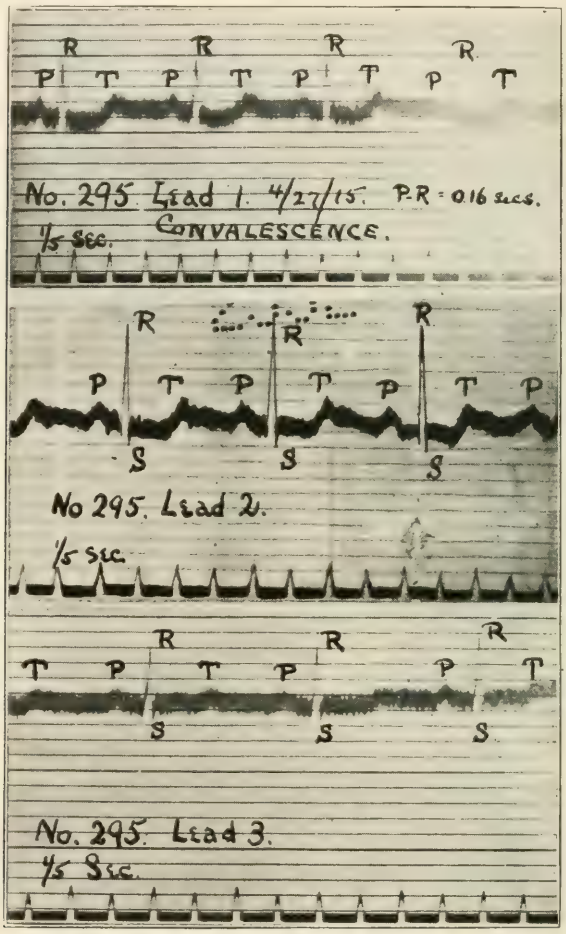

Fig. 2 (Case 1).—Electrocardiogram of same patient as in Figure 1, showing normal rhythm during convalescence from pneumonia. Note reappearance of P wave, regular occurrence of R and absence of fibrillation waves. (The print of Lead II, as in a few other instances, has been retouched for purposes of reproduction.)

I. TRANSIENT AURICULAR FIBRILLATION IN LOBAR PNEUMONIA

Case 1.—V. M., a white man, married, 53 years old, a tinsmith by trade, was admitted to the hospital March 17, 1915, on the third day of a typical attack of lobar pneumonia, involving the left lower lobe. A total arrhythmia was noticed on admission, although the patient had never noticed such arrhythmia before and had never to his knowledge had any previous cardiac trouble Cardiac dulness was not increased and there were no valvular murmurs. Except

for two attacks of gonorrhea twenty-five years before, he had never been seriously ill. He had never had rheumatism, tonsillitis or other fever, although a later blood examination gave a positive Wassermann reaction. The systolic blood pressure on admission was 120, diastolic 95. After the reestablishment of normal rhythm, the systolic pressure was 115, diastolic 85.

An electrocardiogram (Fig. 1) taken on the day of admission showed the presence of auricular fibrillation (of the coarse type), absence of the P wave and a moderate degree of arrhythmia. The form of the electrocardiogram shows no other deviation from the normal, except that the T wave is inverted in Lead III. Tincture of digitalis (0.6 c.c. three times a day) was begun at once and continued during the patient's stay in the hospital of more than a month. Although the pneumonic crisis was reached in four days after admission, with normal resolution of the involved lobe, the pulse rate remained over 100 for another ten days. The arrhythmia became less and less marked, until one month after admission, with the pulse rate varying between 60 and 90, arrhythmia was imperceptible. An electrocardiogram (Fig. 2) taken at this time showed a regular rhythm, with the reappearance of the P wave. The T wave in Lead III is no longer inverted and is more pronounced in the other two leads than in the former record. The patient was discharged in good condition and since then has had no return of any cardiac irregularity. A polygram (Fig. 3) taken three months later revealed a regular radial pulse (rate 62 beats per minute) with a normal jugular pulse. The fact that the myocardium had not yet returned to normal, however, was shown by the persistence of pretibial edema and dyspnea on exertion.

Fig. 3 (Case 1).—Normal polygram three months after pneumonia. Note regular radial rhythm and normal "a, c, v" type of venous pulse, with prominent "a" wave.

Summary of Case.—A patient in the third day of an attack of lobar pneumonia was found to have auricular fibrillation with considerable arrhythmia, although there had been no previous history of heart disease. After recovery from the pneumonia, the arrhythmia gradually decreased, until one month later the electrocardiogram showed a normal P wave and regular rhythm. The exact time at which the auricle began again to beat coordinately was not determined, but was apparently not accompanied by any noticeable subjective symptoms or change in rate. That the return to a normal rhythm was permanent is shown by polygraphic records taken three months later.

II. TRANSIENT AURICULAR FIBRILLATION OF NERVOUS ORIGIN IN SYPHILITIC MYOCARDITIS

Case 2.—B. A., a white woman, married, 38 years old, was admitted to the hospital March 2, 1915, for the removal of a uterine fibroid. She had had measles, mumps, appendicitis and typhoid, but had totally recovered from each, and had otherwise been healthy. Her husband was living and well, but she had had no children, one miscarriage, and the Wassermann reaction was strongly positive. She had never complained of any cardiac trouble until three

weeks before admission, at which time after a hard day's work she had an attack of palpitation, dyspnea and irregular heart action. Another attack occurred the next evening and the symptoms continued more or less marked until admission to the hospital. On the day of admission she had a similar

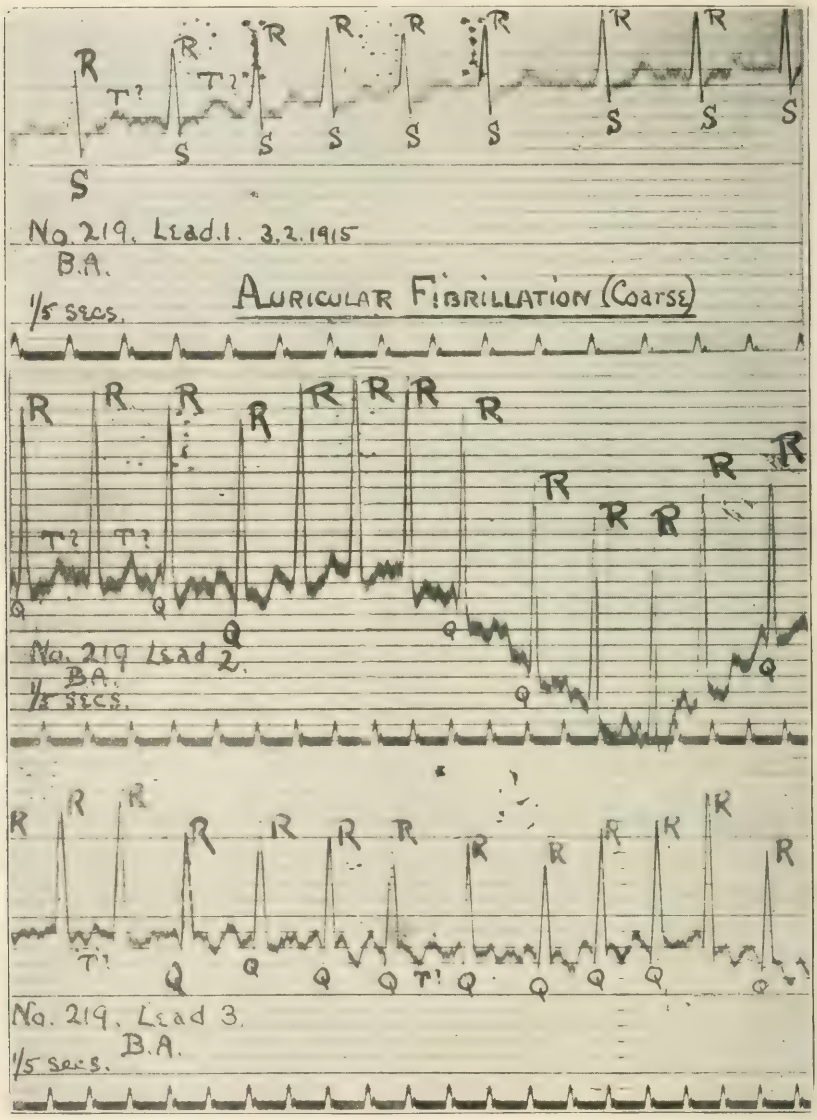

Fig. 4 (Case 2).—Electrocardiogram of Mrs. B. A., taken March 2, 1915, showing transient auricular fibrillation in syphilitic myocarditis. Note same disturbances of mechanism as in Figure 1.

attack, but more serious than any previous one, and the extreme rapidity and irregularity of the heart action necessitated the abandonment of the operation. The patient attributed this attack to the nervous excitement aroused by contemplation of the operation.

At the time of the electrocardiographic study she was in a very nervous state, with warm, flushed skin, and marked tremor of the hands. The radial pulse was distinctly irregular, rapid (180 per minute), quick, full, with increased tension, the wall slightly sclerotic. The cardiac dulness was slightly increased

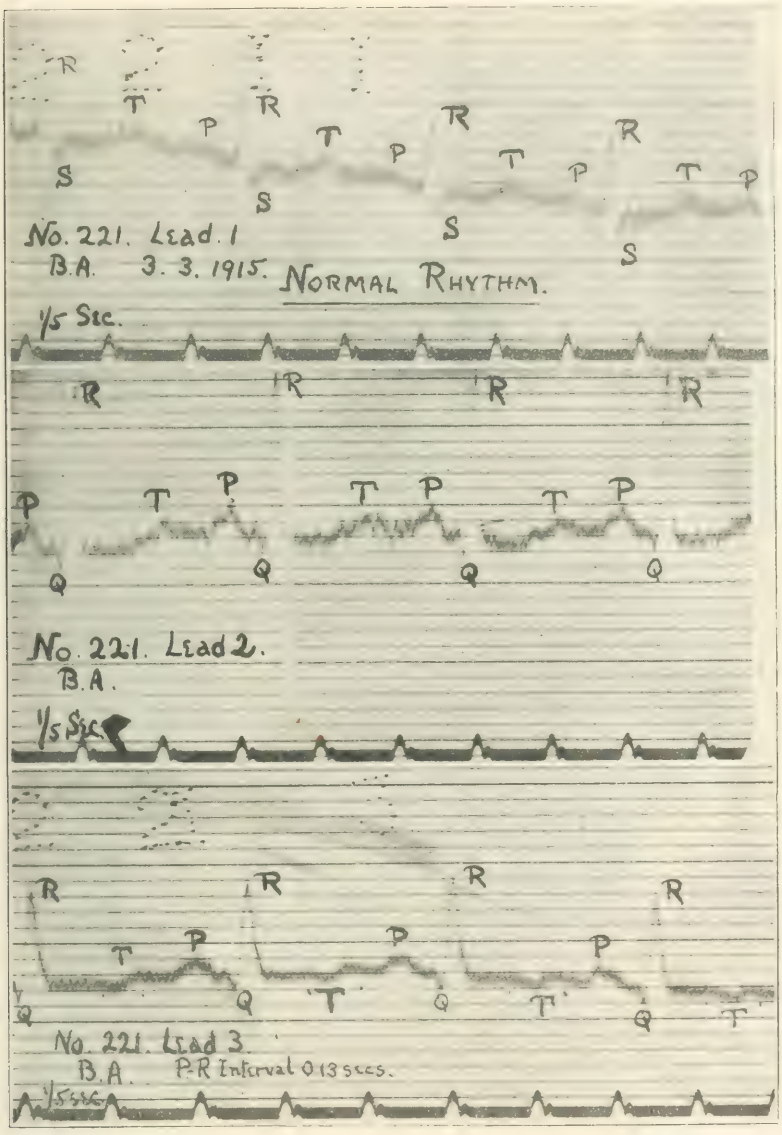

Fig. 5 (Case 2).—Electrocardiogram of same patient as in Figure 4, taken March 3, showing normal rhythm.

to the left, the apex beat distinct in fifth space, 12 cm. from the mid-line. There was a distinct apical systolic murmur transmitted to the axilla, with accentuated second aortic and pulmonic sounds. An electrocardiogram (Fig. 4) showed the arrhythmia to be due to an auricular fibrillation of the

coarse type. With the fear of operation removed, and after a quiet night in bed, the patient awoke the next morning without any disagreeable subjective sensations, and the pulse was regular and much slower. The systolic blood pressure, which during the attack of fibrillation had been 165, was found during the period of regular rhythm to be 132. The diastolic fell from 85 to 78.

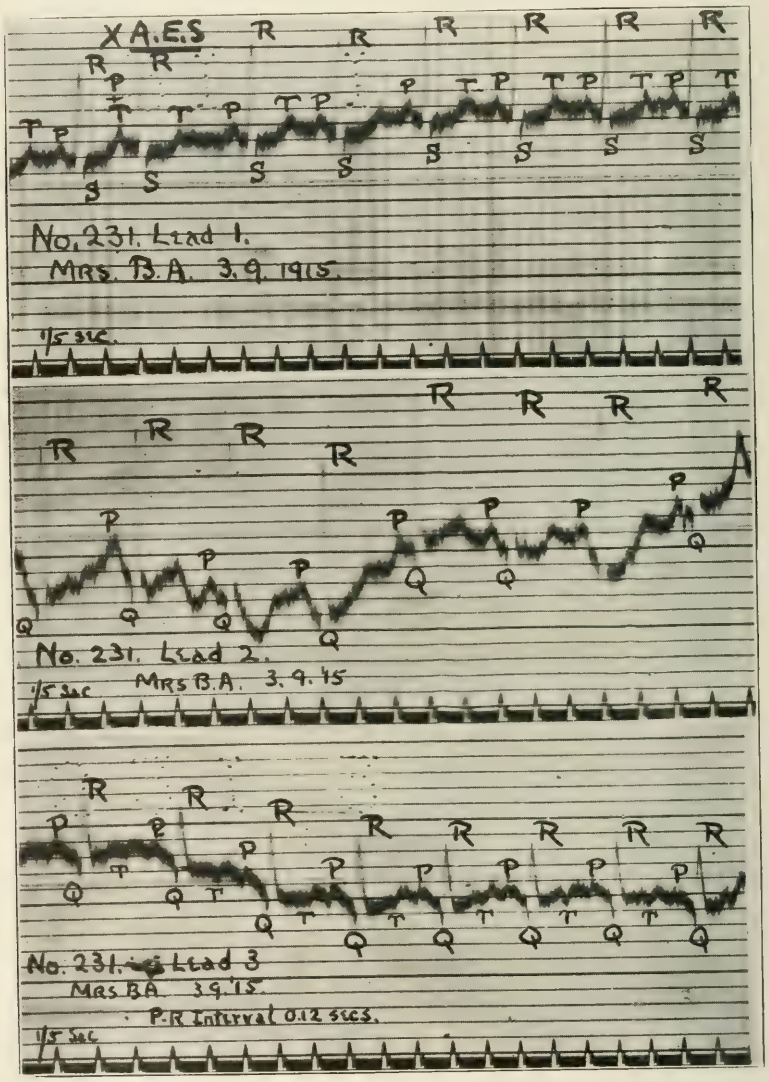

Fig. 6 (Case 2).—Electrocardiogram of same patient as in Figure 4, taken March 9, showing normal rhythm occasionally disturbed by an auricular premature contraction.

An electrocardiogram (Fig. 5) taken the same morning showed a regular rhythm, with a normal P wave. The complexes were practically the same as in the former record (the more rapid passage of the film being shown by the increased intervals of the time marker), except that systole (as indicated by

the end of T) lasted more than 0.3 second and was immediately followed by the next P wave. For several days the patient's improvement continued, the pulse being either quite regular or showing only an occasional slight irregularity. The nature of this irregularity is shown in Figure 6 to be due to an occasional extrasystole. Although there is practically a complete compensatory pause, this is probably an auricular extrasystole merging with the preceding T, because the following ventricular complex shows no ectopic origin.

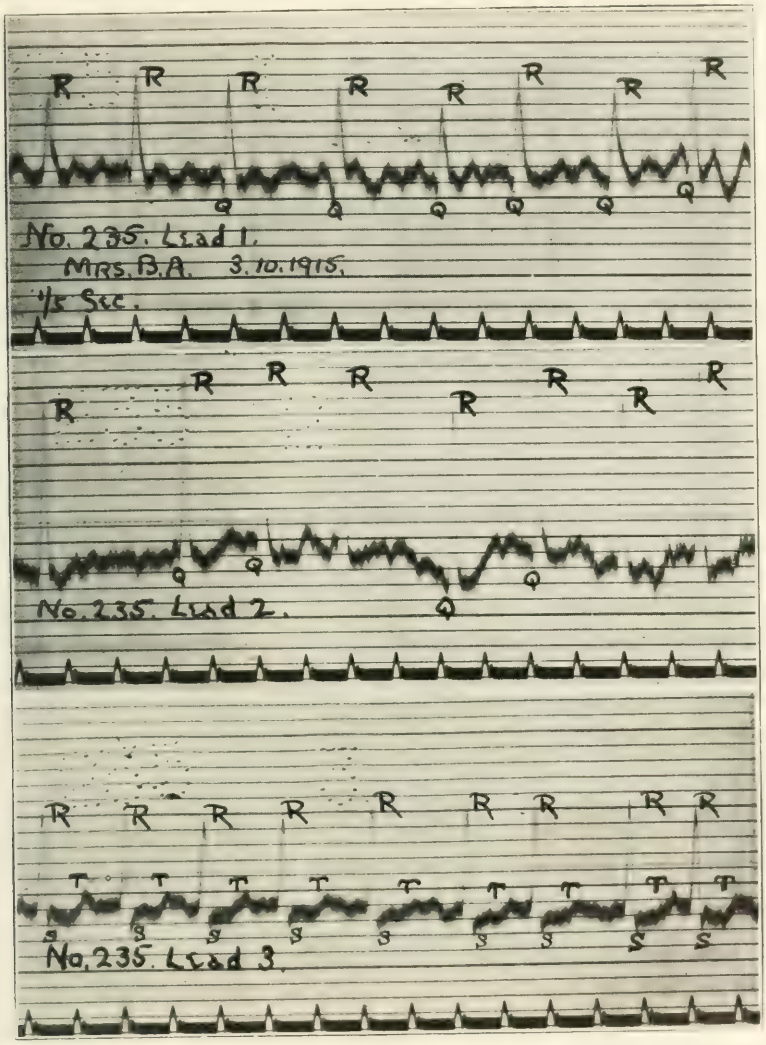

Fig. 7 (Case 2).—Electrocardiogram of same patient as in Figure 4, taken March 10, showing another period of transient auricular fibrillation.

After one week's improvement, the patient awoke one morning from a terrifying dream, and felt her heart pounding violently. Auscultation disclosed a total arrhythmia, with disappearance of all murmurs, a cardiac rate of 130, and a pulse deficit of 50. The systolic pressure was found to have risen to 155, the diastolic remaining at 70. An electrocardiogram (Fig. 7) showed that

coarse fibrillation had again supervened. In Lead I, especially, the fibrillatory waves were so marked and regular that at first the condition of auricular flutter was suggested. This was rejected, however, as the rhythm of the waves of fibrillation was not absolutely regular and the ventricular response was totally irregular, and not explainable by any combination of heart block. During the same afternoon, the patient suddenly announced that the trouble had stopped, and the rate was found to be much slower (80 per minute) and less irregular. Occasional extrasystoles, however, persisted for forty-eight hours. After one week of normal heart action, the patient was returned to the surgical wards for myomectomy and from this time on she flatly refused to allow further cardiac examination.

It is of interest that the patient later volunteered the information that she had had a strong psychic disturbance before each cardiac attack. It is of course possible for a third and unknown factor to have been responsible for both the nightmare and the paroxysmal attack of fibrillation, but the presumption is strong that the cardiac attack was induced by nervous excitement. The chronic endocarditis, enlarged heart and positive Wassermann would all indicate a basic myocardial involvement requiring only the nervous excitation to produce the paroxysm of fibrillation. The appearance of auricular extrasystoles for a few days after each attack is also of interest. It is impossible to say whether these also were of nervous origin or a sign of myocardial degeneration, but here again the time of their appearance affords a strong presumption that the psychic element was at least one factor in their production. A recent report, one year after the period of observation, states that the patient is now in a state of chronic decompensation and that the arrhythmia has become permanent.

Summary of Case.—In a highly excitable, nervous woman, on several occasions strong emotional excitement was observed to be followed by transient attacks of auricular fibrillation. Though the blood pressure was higher during the periods of fibrillation, the state of the pressure just preceding the attacks could not be determined. After the normal auricular activity had returned, the regular rhythm was disturbed for one or two days by occasional auricular extrasystoles. After repeated attacks during the next year, the fibrillation, which had a probable syphilitic myocarditis as a basis, became permanent.

III. TRANSIENT AURICULAR FIBRILLATION OF TOXIC ORIGIN

Case 3.—W. W., a white man, single, aged 40 years, was referred to me for examination on Oct. 12, 1915, by Dr. Newlin, on account of extreme palpitation, dyspnea and arrhythmia of two days' duration. One brother had died of heart disease, following over-indulgence in alcohol, and there was a general family tendency toward overeating and overdrinking. Except for occasional attacks of tonsillitis, the patient had not had any severe infections, but had always eaten too much, and had been a steady consumer of alcohol, but seldom to the point of intoxication. For years he had had some distress after eating and had occasional attacks of heartburn. He had always considered himself in excellent health, however, had not overworked, and had been able to undertake violent exercise without the slightest embarrassment.

The present illness began two months previously while the patient was on a hunting trip in the Rocky Mountains (altitude 5,000 feet). Following an attack of acute bronchitis, the patient noticed that he easily became dyspneic and tired, and that his heart occasionally "skipped" beats. The trip was abandoned, and with appropriate treatment the symptoms disappeared. Systolic blood pressure at this time was 150. In three weeks' time the patient felt

entirely well, except for a mild afebrile tonsillitis, which persisted for several weeks. On a carbohydrate-poor diet he succeeded in losing 50 pounds and the systolic blood pressure dropped to 140. He then began three days of increased alcohol consumption, and became nervous and irritable for several days, but without cardiac symptoms. Then without adequate explanation, after one week of total abstinence, extreme palpitation and arrhythmia developed, with dizziness on standing. The systolic pressure at this time was only 110, diastolic 90. This attack had continued for the two days immediately preceding his visit to the hospital, but he had improved sufficiently to walk without distress.

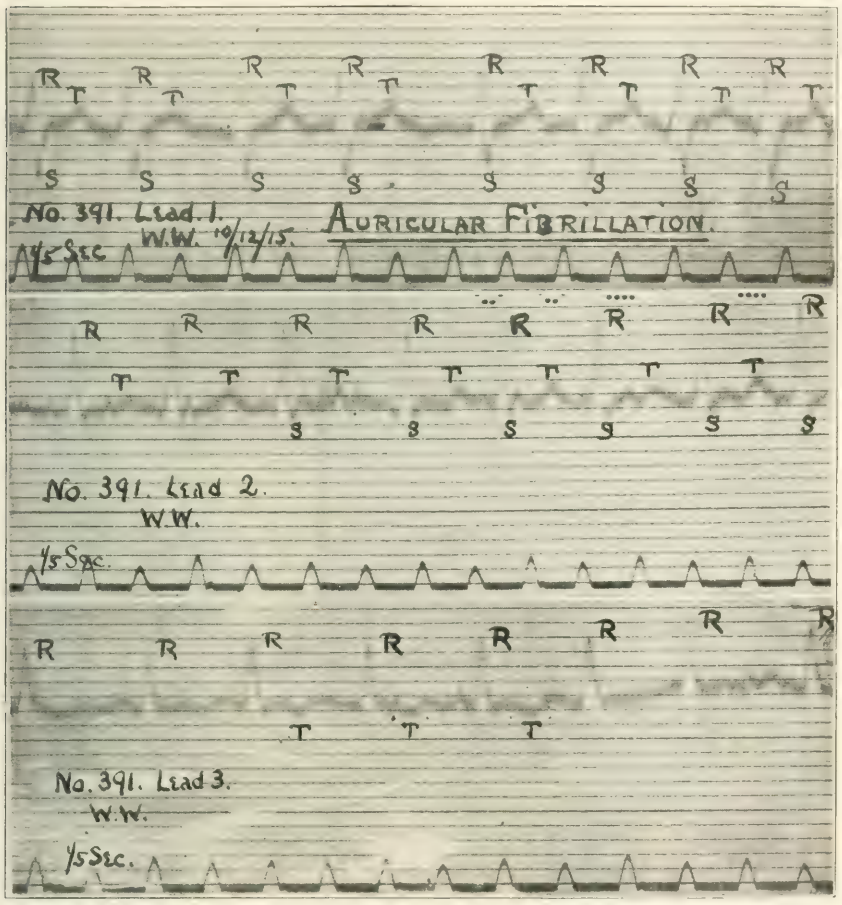

Fig. 8 (Case 3).—Electrocardiogram of patient W. W., who had no discoverable organic lesion, showing transient auricular fibrillation of toxic origin

Physical Examination.—The patient was a large, powerful, well-nourished man, weighing 258 pounds. Although normally rather lethargic, he was at that time apprehensive and slightly dyspneic. The eyes were negative. The tongue was moderately coated, the tonsils red and swollen, but without exudate. There were irregular heavings of the neck, but no distinct venous pulsation. The pulse rate was about 120 and very irregular in force and rhythm. The vessel wall was indefinitely palpable. The heart rate by auscultation was 160, also irregular in force and rhythm, giving a pulse deficit of 25 per cent. The

apex beat was not visible or palpable; the cardiac dulness extended to the right border of the sternum in the fourth space, and 1 cm. to the left of the midclavicular line at the fifth space. No murmurs were audible, but the muscle sounds were rumbling and of poor quality. Examination of the lungs and abdomen was negative. The legs showed very slight pitting on sustained pressure. Frequent urine examinations were always negative.

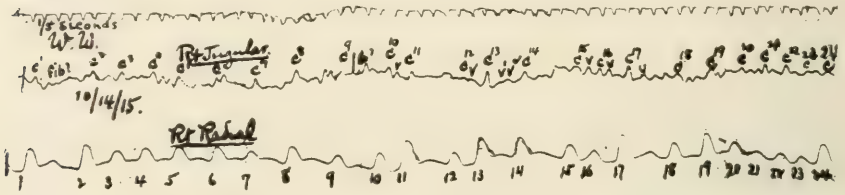

Fig. 9 (Case 3).—The polygram taken immediately after the electrocardiogram shown in Figure 8 exhibits in a more marked degree the irregularities of force and rhythm. The unmarked "c" waves of the jugular pulse indicate the amount of pulse deficit.

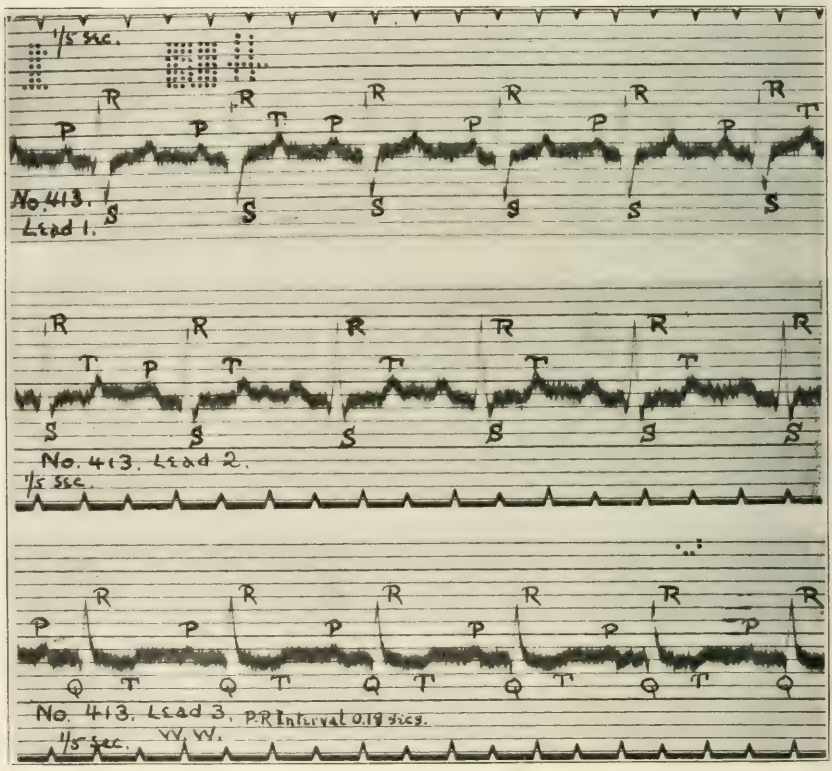

Fig. 10 (Case 3).—Electrocardiogram of same patient as in Figure 8, taken three weeks later, showing normal rhythm.

After three days' treatment, consisting of digipuratum (0.1 gm. four times a day) and local applications to the tonsils, the patient's condition was greatly improved, with cessation of palpitation, dyspnea and cardiac distress. This

was confirmed by Dr. Newlin, who found the heart action and sounds normal and no pulse deficit. The systolic blood pressure was 120 and the diastolic 80. As a result of this improvement the patient resumed his former habits of overeating and overdrinking and in seven months had another cardiac attack lasting three days, which again responded to digitalis. This attack occurred in the middle of the night, while the patient was trying to induce vomiting for the relief of an attack of heartburn. At the present time (May, 1916) he has headaches, gets tired easily, and does not feel so well as before the first attack.

An electrocardiogram (Fig. 8) taken on the patient's first visit showed a distinct arrhythmia with absence of the P wave and with the coarse type of auricular fibrillation. The delirium cordis, however, was much more strikingly shown in the polygraph (Fig 9) taken at the same time, although by this time the patient felt much better and could not say whether or not his heart action was irregular. An electrocardiogram (Fig. 10) taken three weeks later showed a normal regular rhythm with well-developed P wave. The form of the ventricular complex is but little changed from that of the former record.

Summary of Case.—In an adult man, without previous signs of cardiac disease, but with a history of heartburn and chronic overindulgence in food and alcohol, signs of slight cardiac decompensation developed three months before observation. After a short period of improved health, auricular fibrillation with marked cardiac symptoms developed without apparent adequate cause. This persisted for three days, but disappeared under appropriate treatment of rest, digitalis, and local treatment of a subacute tonsillitis, and up to the present time (eight months) has not reappeared, except for one other transient attack lasting for three days. An underlying myocardial weakness is probably in this, as in the other cases discussed in this series, an important factor. While it is impossible absolutely to identify the determining cause of the attack of fibrillation, the blame most probably must fall on either alcohol or the subacute tonsillitis. There were very few signs of decompensation at any time and with the removal of the sources of intoxication, the fibrillation ceased; and yet on account of the probable myocardial disease, a recurrence with correspondingly grave prognosis, must be considered as probable.

IV. TRANSIENT AURICULAR FIBRILLATION DURING DECOMPENSATION IN PANCARDITIS

Case 4.—J. P., a white man, single, 18 years old, was admitted to the hospital Feb. 16, 1916, during an attack of severe decompensation, superimposed on chronic valvular disease, cardiac hypertrophy and chronic nephritis. The chief complaints were dyspnea, cough, edema of buttocks and extremities. Although cardiac symptoms had been present only four years and then occurred without determined adequate cause, it is probable that the cardiac disease started during a severe undiagnosed illness in infancy, which lasted eighteen months. He also was said to have had measles three times during childhood, but his past history and family history is otherwise negative. Although he had had two or more attacks of decompensation before this, he was "passed" by a railroad physician two and one-half years before. The patient presented the usual signs of a decompensated heart disease of long standing, with flushed face, bulging precordium, distended veins, tender liver, ascites and right-side hydrothorax. His heart was enlarged both to the right and to the left and

a loud double mitral murmur was audible with an accentuated second pulmonic sound. The systolic blood pressure varied between 110 and 132; the diastolic between 93 and 110. The venous blood pressure equaled 14 cm. (water). The urine has always contained a large amount of albumin and

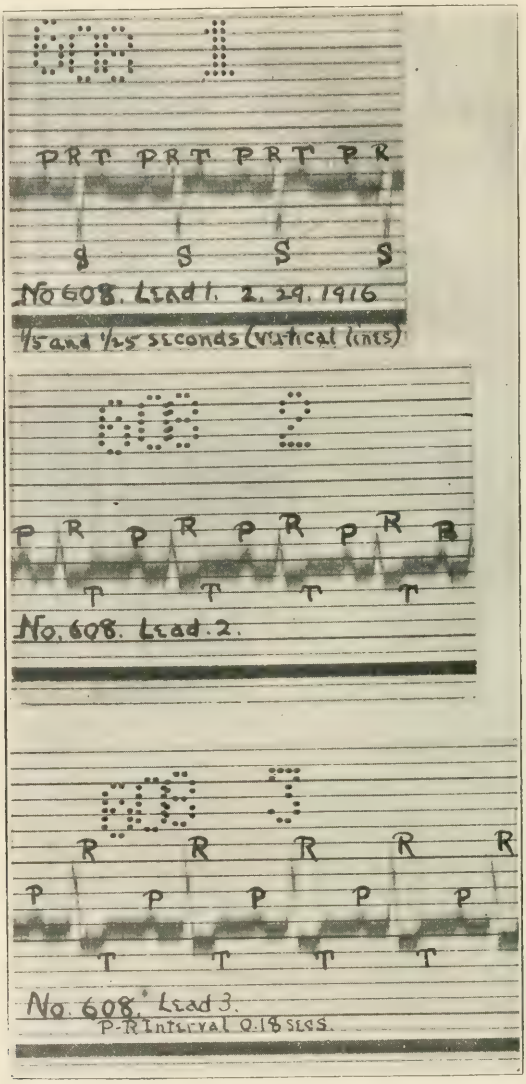

Fig. 11 (Case 4).—Electrocardiogram of patient J. P., a case of fatal mitral stenosis with decompensation, taken Feb. 29, 1916, showing normal rhythm, with right ventricular preponderance.

occasional hyaline casts. The phenolsulphonephthalein elimination was 40 per cent. The blood counts were normal. The Wassermann reaction was negative. An orthodiagram showed increase of cardiac shadow both to the right and left.

An electrocardiogram (Fig. 11) taken the day after admission showed a regular rhythm with well-defined P wave, and the evidences of preponderating hypertrophy of the right ventricle; the P-R interval was 0.18 second. In spite of absolute rest in bed, digitalis and codein medication, the patient's

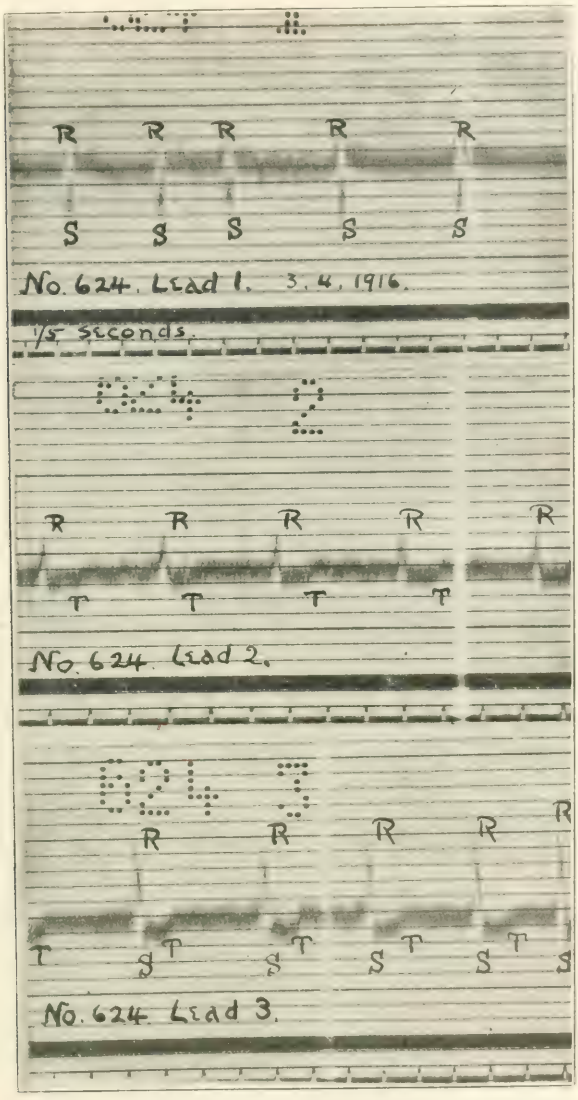

Fig. 12 (Case 4).—Electrocardiogram taken March 4, 1916, of same patient as in Figure 11, showing transient auricular fibrillation. Though the fibrillation has not been of long duration, the waves of fibrillation are not visible.

condition became steadily worse, with increased edema, insomnia, nausea and vomiting. An electrocardiogram (Fig. 12) taken twelve days later failed to show any change, and did not show any of Cohn's digitalis effects. A third record (Fig. 13), taken four days later, revealed the presence of auricular fibrillation.

although no arrhythmia was suspected until the prints of this record became available for study. Another record was taken three days later and it was found that the rhythm had again become regular with reappearance of the P wave. The day before this record was made (that is, two days after recording auricular fibrillation) the signs of acute pericarditis (loud to and fro fric-

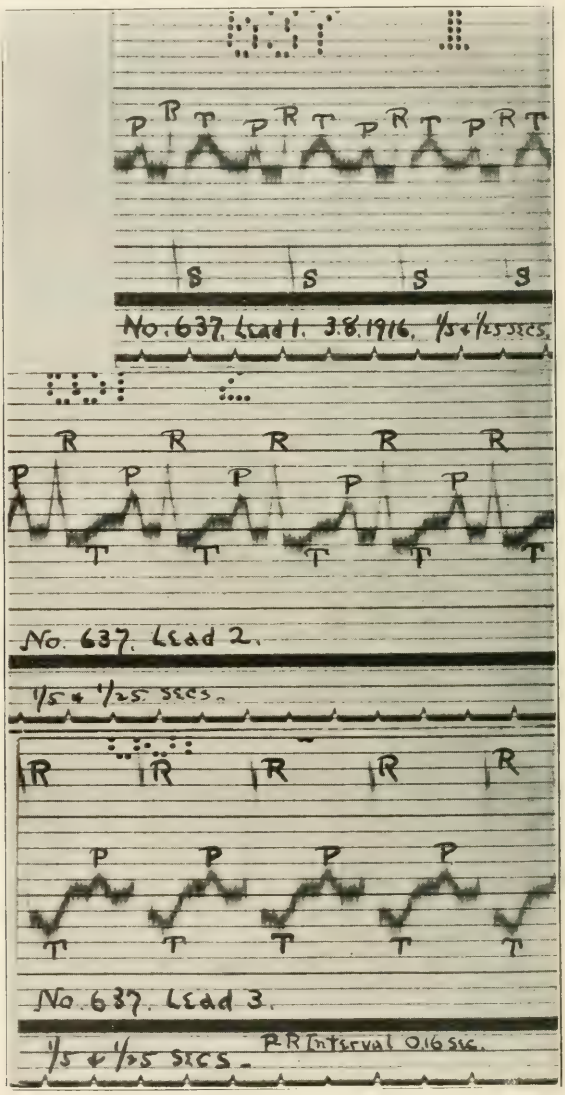

Fig. 13 (Case 4).—Electrocardiogram taken March 8, 1916, of same patient as in Figure 11, showing normal rhythm again, with large P Wave.

tion rub) became manifest, with increase in pulse rate (110 to 140), development of fever, and general aggravation of symptoms. Although these signs were definitely not present in an examination made the day fibrillation was determined, nevertheless an infection, not sufficiently advanced to cause signs,

cannot be ruled out as the added insult that provoked the auricular fibrillation. From this time on the patient became steadily worse, dying in four days from heart failure.

At necropsy the following conditions were found: Concentric hypertrophy of the right ventricle (weight 270 gm.); concentric atrophy of the left ventricle (weight 70 gm.); hypertrophy and dilatation of the right auricle, and concentric hypertrophy and chronic mural endocarditis of the left auricle; chronic mitral endocarditis (extreme stenosis and thickening, with sclerosis of chordae tendineae and tips of papillary muscles); acute fibrinous pericarditis, and (slight) acute vegetation mitral and mural endocarditis; chronic fibrous pleurisy and pericarditis (basal); general chronic passive congestion of viscera; hydrothorax (bilateral) and ascites. Histologic examination confirmed these findings and showed surprisingly little myocardial fibrosis.

Summary of Case.—A boy of 18, suffering with mitral stenosis, was admitted to the hospital in an extreme stage of decompensation, but with normal cardiac rhythm. His condition became steadily worse and eventually auricular fibrillation developed, and the next day an acute pericarditis was found to be present. Fibrillation was replaced after three days by normal rhythm, but death occurred four days later from cardiac failure with persistence of the acute pericarditis. At autopsy an extreme mitral stenosis, with cardiac hypertrophy and dilatation was found.

V. DEVELOPMENT OF PERMANENT AURICULAR FIBRILLATION

In two cases the onset of auricular fibrillation occurred while the patient was under observation. Although the first attack in each of these cases proved to be permanent, they are included in this series on account of certain prognostic indications that they offer.

CASE 5.—L. Z., a Polish woman, 33 years old, married, was admitted to the maternity ward of the University Hospital, Jan. 6, 1915, in her fourth pregnancy. The first three pregnancies were normal, but after the birth of the third child, she had a severe attack of "grippe," was in bed after that for three months, and was told by her doctor at that time that she had heart trouble. She had had scarlet fever, measles, chickenpox and typhoid as a child, but had never had sore throat, acute rheumatic fever, or any symptoms of heart disease. Her social and family histories were negative.

Her present attack of decompensation began about the seventh month and gradually grew worse as pregnancy progressed, until in the ninth month labor was induced by Dr. Hirst on account of extreme dyspnea and edema. After delivery her symptoms were much improved, but one week later an attack of intense dyspnea ensued, with precordial pain and a dry, nonproductive cough. She also suffered from anorexia, constipation, headache, weakness, and pain in both breasts (baby had been weaned two days before).

Physical Examination.—When transferred to the medical ward, the usual signs of marked decompensation were found. The pulse was regular, rapid, quick, fair volume and tension and the wall of the artery not sclerosed. The systolic blood pressure was 130, the diastolic 80. There were forcible arterial pulsations in the neck, with apparently the ventricular type of venous pulse. The cardiac impulse was forcible, 17 cm. from the midline (following curve of chest), almost in midaxilla, in the fifth interspace. The cardiac dulness extended 5 cm. to the right of the midline, 17 cm. to the left. At the apex the first sound was loud and preceded by a presystolic murmur and thrill, a systolic

murmur also being heard nearer the sternum. The second pulmonic was accentuated, the liver enlarged and palpable and râles audible at the bases of the lungs. There was generalized edema, ascites and bilateral hydrothorax. The blood showed a moderate anemia. The specific gravity of the urine was 1.028, and it contained a cloud of albumin, and hyaline, granular and leukocytic casts. The phenolsulphonephthalein elimination was 47 per cent. The Was-

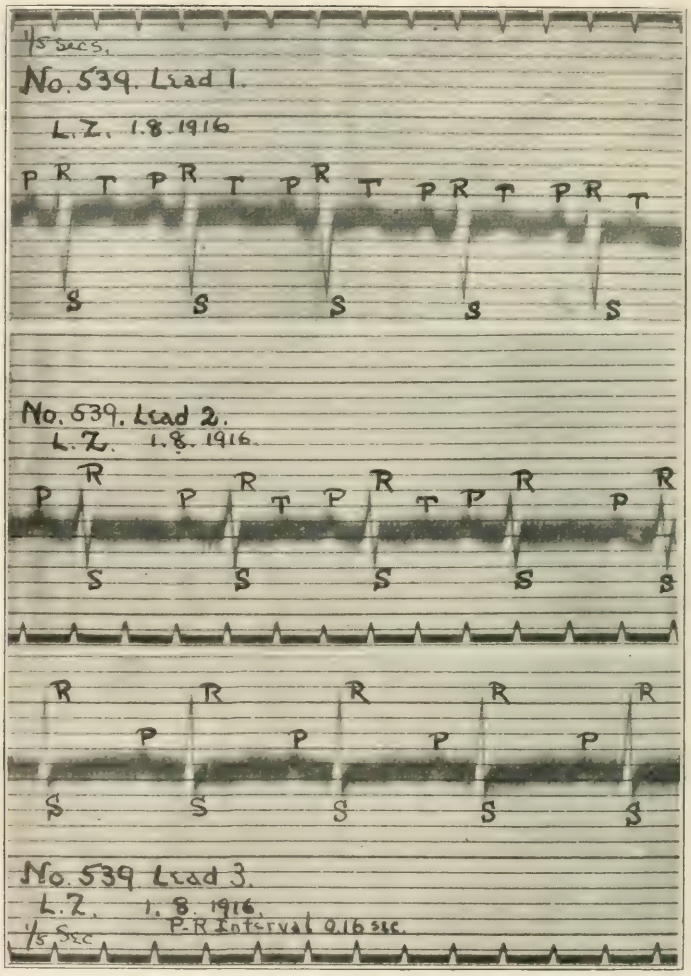

Fig. 14 (Case 5).—Electrocardiogram of patient L. Z., a case of fatal mitral stenosis with decompensation, taken Jan. 8, 1916, showing normal rhythm with right ventricular preponderance.

sermann reaction was negative. An electrocardiogram (Fig. 14) showed a regular rhythm with preponderance of the right ventricle and poorly defined T waves.

Course.—The patient improved slightly under digitalis and hypnotics, but four days after admission she had another attack of dyspnea and tachycardia. The pulse at the wrist was uncountable, the heart rate by auscultation was 196 and apparently regular. The following day, after a good night's rest, the

patient seemed much better and the pulse rate was lower. The day after this, arrhythmia was first noted, and the electrocardiograph (Fig. 15) established the diagnosis of auricular fibrillation. Although there is no record of the heart rhythm on the intervening day, it is probable that the rapid period was due to auricular flutter, which progressed to fibrillation. The course of the physical signs and several electrocardiograms taken in the next few days

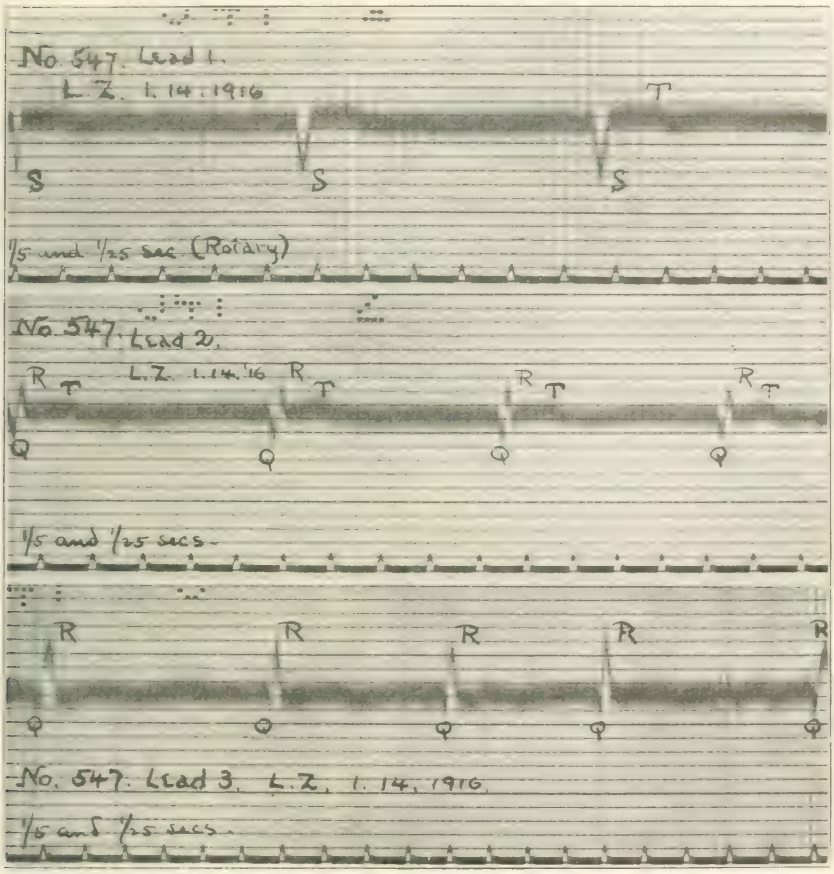

Fig. 15 (Case 5).—Electrocardiogram of same patient as in Figure 14, taken January 14, showing permanent auricular fibrillation. Though this symptom has not been of long duration, the waves of fibrillation are not visible.

confirmed the diagnosis of fibrillation and recorded the response of the heart to digitalis (slowing of rate, lessening of arrhythmia, change in form and Q and T waves). At no time were the waves of fibrillation of the coarse type. The patient, however, failed to improve clinically, and succumbed in three days with the signs of acute dilatation. Necropsy was refused.

Summary of Case.—A woman with mitral stenosis of at least four years' duration had such severe signs of decompensation during her fourth pregnancy that labor had to be induced. She improved during the first week of the puerperium, but then a second and more severe

stage of decompensation set in. In the third day of this attack a very rapid pulse rate was initiated (auricular flutter?) and this progressed to auricular fibrillation, which persisted until death three days later.

The development of auricular fibrillation after a transient period of flutter has been frequently observed; in fact the administration of large doses of digitalis has been recommended in cases of auricular flutter in the hope that the disturbance may pass on to fibrillation and thence, perhaps, return to normal rhythm. The contingency must at least be considered, therefore, in the present case that digitalis was a contributing factor to the causation of fibrillation.

VI. DEVELOPMENT OF PERMANENT AURICULAR FIBRILLATION DURING CARDIAC DECOMPENSATION

Another case is reported in which auricular fibrillation developed after three years occasional observation.

Case 6.—M. H., an American woman, 35 years old, married, was admitted to the University Hospital on March 21, 1916, with the usual signs and symptoms of cardiac decompensation. This was a recurrence similar to those seen in her previous admissions in the spring of 1913 and the autumn of 1914. She had had measles, mumps, scarlet fever and acute articular rheumatism. Her cardiac symptoms were first noted at the time of a second attack of acute polyarthritis thirteen years before, and reappeared during an attack of "grippe" nine years before. For the past four years she has suffered from some shortness of breath and puffiness of the ankles, which on the two occasions mentioned became bad enough to make her seek the hospital. At both these times she improved quickly under hospital care, and she had never noticed any irregularities of her heart further than an occasional dropped beat.

The present illness started two weeks before admission with greatly increased dyspnea, palpitation and pericardial pain. Four days later the patient suffered a "stroke," losing the power of speech and of moving the left arm, but not becoming unconscious. Speech returned after sleep, but the left thumb, index finger and left side of the face have remained numb and weak. Four days after that, sudden pain developed low in the right chest with cough and hemoptysis, and the lesion was later shown by the Roentgen ray to be a pulmonary infarct. Social and family history irrelevant

Physical Examination.—It was found on examination that the patient was more emaciated than on previous admissions; the tongue was dry and coated, with herpes on the lips. The cardiac dulness extended 3 cm. to the right of the midline and 13 cm. to the left. The apex beat was well localized in the fifth space 2 cm. outside of the midclavicular line. There was a harsh systolic murmur, best heard at the apex and transmitted to the base and axilla. No arrhythmia was noted. The liver was palpable 4 cm. below the costal margin and the right kidney was also palpable. There was dulness and râles at the bases of both lungs, but more marked on the right. The leukocytes varied between 10,000 and 14,000; hemoglobin 95 per cent., red blood cells 5,480,000. The urine was acid, specific gravity 1.018, contained a cloud of albumin, urates, but no casts. The Wassermann reaction was negative. The systolic blood pressure varied between 115 and 120, the diastolic between 77 and 90. The signs of decompensation decreased steadily during the patient's stay in the hospital, so that she was able to leave in one month in very good condition. The cardiac arrhythmia, which was first discovered by electrocardiographic examination, was still present, but frequently had been so slight that it could not be detected by simple digital examination of the pulse.

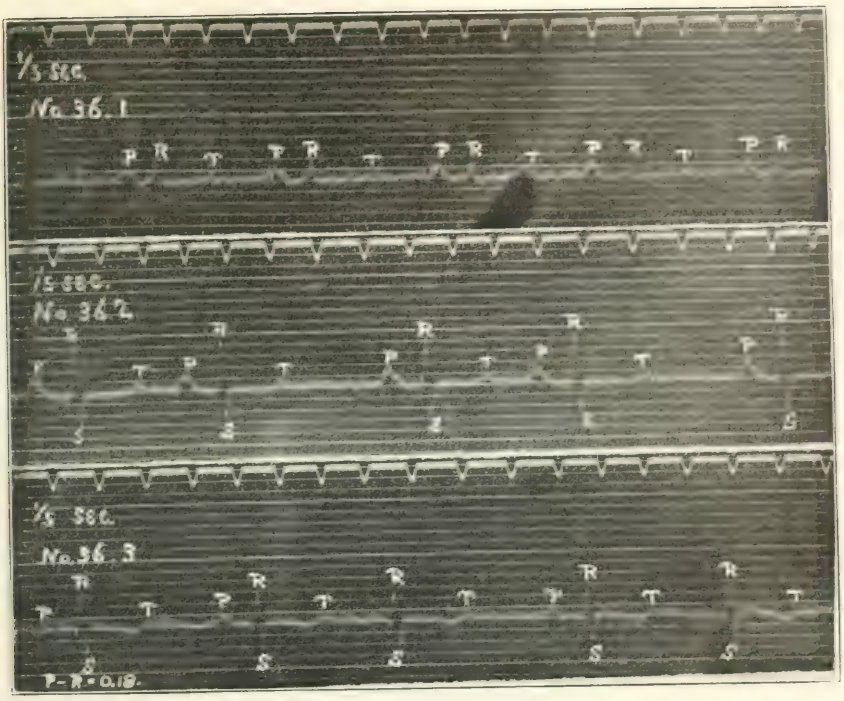

Fig. 16 (Case 6).—Electrocardiogram of patient M. H., a case of mitral stenosis with decompensation, taken April 14, 1913, showing normal rhythm (sinus arrhythmia).

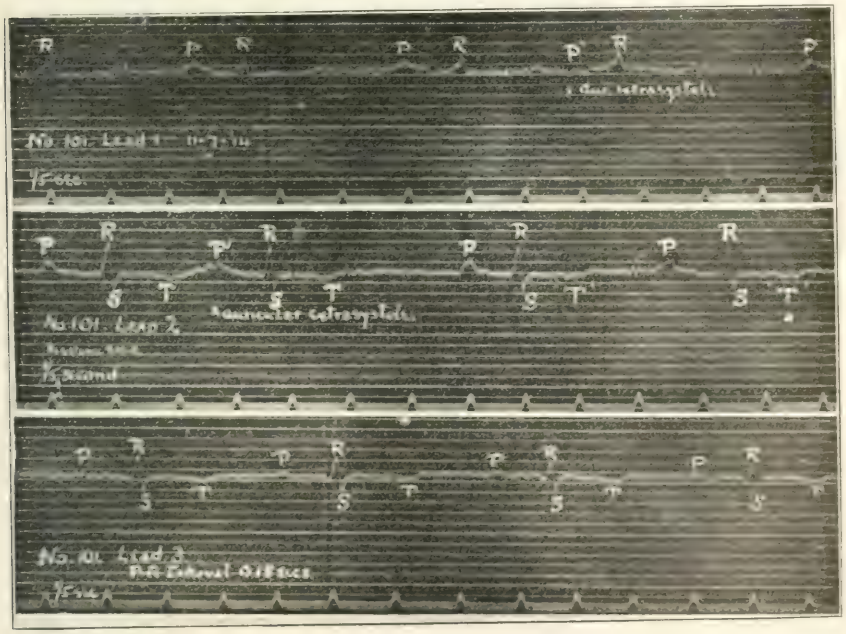

Fig. 17 (Case 6).—Electrocardiogram of same patient as in Figure 16, taken in November, 1914. The figure shows occasional auricular premature contractions.

Electrocardiograms (Fig. 16) were taken during each stay at the hospital. The one taken in 1913 showed a normal rhythm and complexes, with a P-R interval of 0.18 second. No abnormalities of rhythm were noted either during the examination or during the patient's stay in the hospital. The electrocardiogram (Fig. 17) taken in 1914 showed, besides some small changes in the form of the ventricular complex, the same P-R interval as on the first admission, but two definite auricular extrasystoles in addition. The large P wave

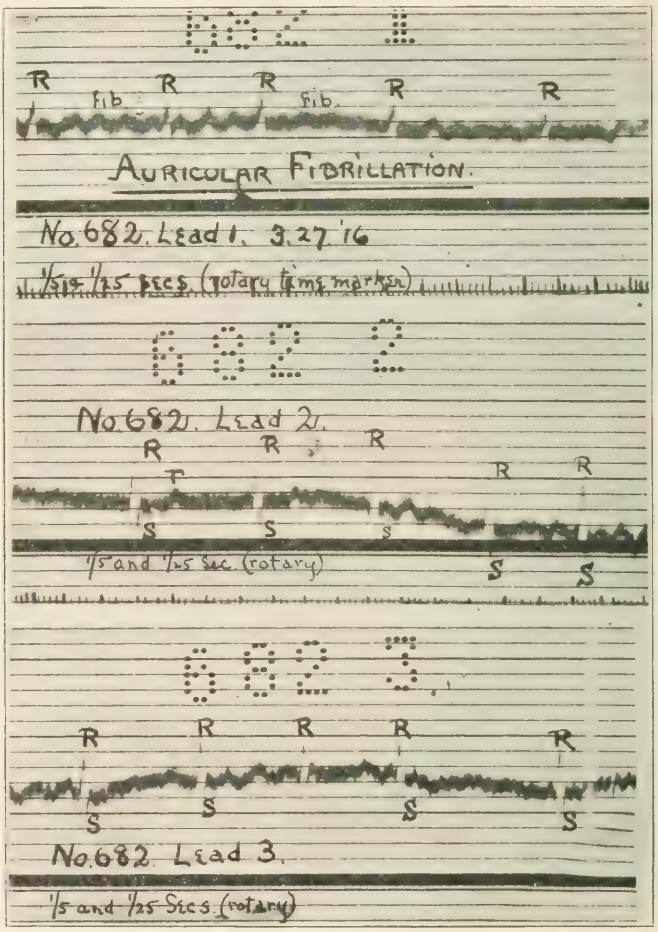

Fig. 18 (Case 6).—Electrocardiogram of same patient as in Figure 16, showing permanent auricular fibrillation (waves of coarse type).

characteristic of mitral stenosis persisted. On the patient's last admission in March, 1916, electrocardiograms (Fig. 18) taken on several occasions constantly showed a coarse type of auricular fibrillation. The form of the ventricular complexes, however, had changed very little from that of the two former admissions. Although the patient improved steadily from a clinical point of view, fibrillation persisted with a gradual decrease of the coarseness of the fibrillation waves.

Summary of Case.—In a case of mitral stenosis of some years' standing with recurrent periods of decompensation, electrocardiographic records were made over a period of three years. At first the rhythm was normal, next was broken by occasional auricular extrasystoles and finally was found to have been replaced by a constant, coarse type of fibrillation. If the history may be relied upon, this probably developed within two weeks of admission to the hospital, when decompensation was further complicated by cerebral and pulmonary emboli and infarct formation.

GENERAL COMMENT

A comparison of the foregoing cases with those mentioned in the literature allows the change from normal rhythm to auricular fibrillation to be subdivided into three types.

In the first group falls the first case of this series, twelve of Cohn's[11] pneumonia cases, all four of those reported by Fahrenkamp, Robinson's[12] recent case, the fourth of Heitz's and the sixth of Fox's series. In these cases the predominant factor was some acute infection or intoxication (pneumonia, septicemia, hyperthyroidism), and the attack of fibrillation was single. No organic cardiac lesion was found or need be presumed, and when the infection or intoxication was removed the rhythm returned permanently to normal.

In the second group, and this comprises the larger number of those cases reported as paroxysmal auricular fibrillation, belong the second and probably the third cases of this report, also the remaining nine of Heitz's, the four of Hornung's, four of Fox's series, and the single cases of Robinson, Popper, and Lewis and Schleiter. At the time of observation all but three of these patients were in the sixth or seventh decade of life, but the onset of attacks when mentioned occurred as follows: Two in the third decade, two in the fourth, five in the fifth, five in the sixth, and six in the seventh decade. The average duration of the condition was over nine years. Both sexes were equally involved. Previous diseases bore no relationship to the condition; even the cardiac condition varied greatly. In eight cases mitral lesions were present, but in ten others no valvular lesion was found. In nearly all, however, there was distinct evidence of myocardial disease. The blood pressure was found increased in seven and not increased in eight. Arteriosclerosis was noted in ten. Factors determining the paroxysms were either absent or widely varying in character. In six, emotional excitement preceded attacks and in two others they were attributed to a general increase in

11. Cohn, A. E.: Certain Phases of the Action of Digitalis in Pneumonia, Meeting of Am. Soc. for the Advancement of Clin. Investigations, Washington, D. C., May 8, 1916, unpublished.

12. Robinson, G. C.: Transient Auricular Fibrillation in a Healthy Man Following Hydrogen Sulphid Poisoning, Jour. Am. Med. Assn., 1916, lxvi, 1611.

the patient's nervousness. In four, attacks were induced by exercise or fatigue, but in three others they nearly always occurred during sleep. Overeating (three cases), defecation, and asthmatic attacks were held responsible in other cases. Many of these factors might be grouped under the head of conditions that raise blood pressure, but in some cases this factor was definitely absent. The duration of the individual attacks was also extremely variable, ranging from a few minutes to several weeks; in most cases, however, they lasted a few hours. In the early stages the attacks tended to be either short or infrequent, the duration and frequency of the attacks increasing as the disease progressed. They usually began abruptly, without premonitory symptoms, and caused more or less severe cardiac embarrassment. The attacks ended either during sleep or with such abruptness that the patient could notice the return to regular rhythm. In only one case were extrasystoles noticed between attacks, and in two cases there occurred also attacks of paroxysmal tachycardia. In this connection Lewis and Schleiter have called attention to the closely related mechanism of auricular extrasystoles, fibrillation and paroxysmal tachychardia. Six patients died while under observation (mostly from cardiac complications during regular rhythm); in five others fibrillation had become permanent; while six of the remaining ten were considered as improved. Venesection, digitalis and quinin have been used successfully and the ordinary treatment of cardiac failure seems advisable.

In a third group, represented by the last three cases of this report and the fourth of Fox's series, the onset of fibrillation should be regarded as but one more link in the chain of cardiac failure. In all these cases the signs of mitral disease with decompensation were prominent and had existed for years. In two cases the first attack of fibrillation proved to be permanent, one of these being preceded by auricular extrasystoles, in one other the permanent period was preceded by one transient period, and in the fourth a transient period lasting three days occurred a few days before death from cardiac failure (normal rhythm). The development of most of the cases of permanent auricular fibrillation is probably of this character, but closer observation and wider use of graphic methods would probably reveal one or more previous transient periods. As auricular fibrillation aggravates the prognosis, energetic treatment should be instituted at these times, in order to delay or avoid the onset of the permanent condition. That this should not include too large doses of digitalis is indicated by the fact that in two cases at least (Case 3 of this report and Robinson's case) digitalis was considered as a possible factor in the production of fibrillation. Its value as a cardiac remedy, however, especially after fibrillation is established, makes it a necessary aid in practically all such cases.

SUMMARY

Four cases are described in which the transition of the cardiac mechanism was observed from normal rhythm to auricular fibrillation and back again. In two others the development of permanent auricular fibrillation was observed. These have been compared with similar cases in the literature.

CONCLUSIONS

Transient auricular fibrillation is a comparatively rare condition, although the more widespread and frequently repeated use of the string galvanometer will probably reveal many more cases than are now available for study.

The change from normal rhythm to auricular fibrillation occurs in three well-defined groups:

1. In the course of an acute infection, such as pneumonia or septicemia, or of an acute intoxication, such as alcohol or hyperthyroidism, or possibly from other temporary causes, one or more attacks of fibrillation may occur for several days, but disappear permanently when the source of intoxication is removed. In this group permanent myocardial damage is probably not present.

2. In another group, probably always associated with underlying myocardial degeneration, paroxysms lasting from a few minutes to many hours or even days, may be induced by a great variety of causes and occur over a period of many years. They tend, however, to become more lasting or more frequent or both, and eventually with the progress of the myocardial disease the fibrillation becomes permanent. Death may occur, however, before permanent fibrillation has ensued, or clinical improvement may take place with the onset of fibrillation. The term "paroxysmal" is most aptly applied to cases of this group.

3. In a third group, in which the signs of valvular or myocardial disease are more prominent, the original change from normal rhythm to fibrillation is liable to be permanent, or at least be preceded by only a few transient periods. A determining factor in such cases is liable to be some cardiac complication, such as pulmonary embolus, acute pericarditis, or the added strain of pregnancy, and may be preceded by a transient period of flutter.

No relationship between the onset of fibrillation and changes in blood pressure could be established.

In the earlier stages of fibrillation the electrocardiogram usually shows coarser waves of fibrillation, so that this evidence, when present, may be guardedly used to influence favorably the prognosis.

The occurrence of fibrillation, while a bad factor in prognosis, does not necessarily indicate either permanency or a fatal outcome. It is of graver significance when it occurs in valvular cases with prominent signs of decompensation, and of least significance in the cases of the first group.

The usual treatment of heart failure (rest in bed, the digitalis group, removal of sources of intoxication, etc.) help to terminate attacks of fibrillation, but excessive doses of digitalis may help to induce this condition.

These cases were studied in the wards and laboratory of the University Hospital, while under the care of Drs. Stengel, Hirst, Anspach and Newlin, to whom my thanks are due.

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